(12)

U.S. Army Environmental Hygiene Agency

USAEHA

PHASE 2
TOXICOLOGICAL STUDY NO. 75-51-0743-88(2)
TRICHLOROMELAMINE
14-DAY RANGE FINDING AND 90-DAY
SUBCHRONIC STUDIES IN RATS
3 AUGUST 1988 - 17 JANUARY 1989

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UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution unlimited.
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: U.S. ARMY ENVIORNMENTAL HYGIENE AGENCY 6b. OFFICE SYMBOL (If applicable): HSHB-MO-T	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code): Aberdeen Proving Ground, MD 21010-5422	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: Natick Laboratories 8b. OFFICE SYMBOL (If applicable): STRNC-YEP	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code): Natick Research, Development and Engineering Center, Natick, MA 01760-5020	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. / PROJECT NO. / TASK NO. / WORK UNIT ACCESSION NO.

11. TITLE (Include Security Classification)
Trichloromelamine, Phase 2 - 14-Day Range finding and 90-Day Subchronic Studies in Rats

12. PERSONAL AUTHOR(S)
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13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Final	FROM 3 Aug 88 TO 17 Jan 89	92/11/13	67

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Trichloroemelamine, toxicity, 14-Day, 90-Day

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The subchronic study examined the toxicity of the food service disinfectant trichloromelamine (TCM) in rats following oral administration for 90 days. Associated with the administration of TCM in rats were lesions in the stomach and trachea, while also causing engorgement of the small blood vessels of the adrenals, brain, kidneys, liver, lung and pituitary. The no observed adverse effect level in the 90-day study was 30 mg/kg/day. Trichloromelamine should be considered moderately toxic when ingested acutely, and continuous ingestion could cause serious health effects.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☑ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	UNCLASSIFIED

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
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DD Form 1473, JUN 86 — Previous editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010-5422

REPLY TO
ATTENTION OF

EXECUTIVE SUMMARY
PHASE 2
TOXICOLOGICAL STUDY NO. 75-51-0743-88(2)
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1. PURPOSE. Information provided by this study will be used to establish safety criteria for human exposure. A preliminary 14-day range finding study was conducted to determine the effects of oral administration of TCM to establish reasonable dosage levels for the 90-day study. The subchronic study examined the toxicity of the food service disinfectant trichloromelamine (TCM) in rats following oral administration for 90 days.

2. CONCLUSIONS. Associated with the subchronic oral administration of TCM in rats were lesions in the stomach and trachea while also causing engorgement of the small blood vessels of the adrenals, brain, kidneys, liver, lung and pituitary, as well as pulmonary edema. The no observed adverse effect level for the oral administration of TCM to rats was 30 mg/kg/day in the 90-day study. Trichloromelamine should be considered moderately toxic when ingested acutely, and continuous ingestion could cause serious health effects.

3. RECOMMENDATIONS. Proceed with the use of TCM as a food service disinfectant. Use of TCM as directed will limit overexposure and resulting health effects.

DEPARTMENT OF THE ARMY
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1. REFERENCES. See Appendix A.

2. AUTHORITY.

a. Letter, HSCL-P, 26 August 1987, subject: Toxicity Clearance for Trichloromelamine, Active Ingredient in Disinfectant, Food Service (MIL-D-11309).

b. Letter, United States Environmental Protection Agency (EPA), 4 Mar 1987, subject: Data Call-In Notice for Subchronic Toxicological Data for Antimicrobial Pesticide Active Ingredients.

3. PURPOSE.

a. A preliminary 14-day range finding study was conducted to determine the effects of oral administration of trichloromelamine (TCM) over a 14-day period. Results of this study were used to establish appropriate dosage levels for the subsequent 90-day study.

b. To determine the toxicity of the food service disinfectant TCM in rats following oral administration for 90 days. Information provided from this study will be used to establish safety criteria for human exposure.

4. BACKGROUND.

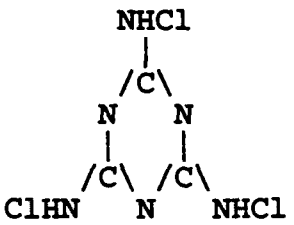
a. The U.S. Army Environmental Hygiene Agency (USAEHA) was initially tasked to evaluate the acute toxicities of TCM in July 1976, USAEHA Study Nos. 75-51-0124-76 and 75-51-0195-84 (reference 1). Mutagenicity, aquatic lethality studies, dominant lethal, and Shimkin Mouse assays were completed between 1984 and 1987 under USAEHA contract Study Nos. 75-51-0195-87 and 75-51-0668-86 (references 2-6).

b. In 1987, the U.S. Environmental Protection Agency (EPA) issued a Data Call-In Notice for subchronic toxicity data on all antimicrobial pesticide active ingredients. A search of available literature revealed a lack of subchronic animal toxicity data for TCM. This 90-day study was initiated to

further assess the subchronic toxicity of TCM, and to support required testing set forth by the EPA to maintain the Army's registration of TCM as a food service disinfectant.

5. MATERIALS AND METHODS.

a. Test Substance. The test material, trichloromelamine (CAS Registry Number 7673-09-8), technical grade, lot number 2342, was procured from Dorex Inc., 121 Ontario St., Frankfort, IL 60423. Trichloromelamine is a fine, white to light tan powder with a solubility in water of 0.34 grams/liter at 25 °C. The molecular formula is C3-H3-Cl3-N6, with a molecular weight of 229.47, and a chemical structure as follows:



Trichloromelamine is an oxidizing compound that reacts with reducing agents or organic compounds. Mixtures of TCM with rodent chow will produce a reaction that binds all free chlorine. Analysis of feed by free chlorine determination (Standard Methods 408A - Appendix B) to ascertain TCM concentrations in the feed was therefore not possible. Gavage was chosen as the method of compound administration to enable dosages to be verified by analytical means. Due to the low solubility of TCM in water, suspensions of the compound in water were used to achieve necessary concentrations, while keeping dosing volumes within guidelines.

b. Animals. Young, adult Sprague-Dawley male and female rats used in the studies were supplied by Charles River Laboratories Incorporated, Wilmington, Massachusetts. Female rats were both nulliparous and nonpregnant. Animals were toe clipped for identification purposes.

c. Diet. Certified Rodent Ration, manufactured by Zeigler Brothers, Inc., Gardners, Pennsylvania (Appendix C), was given ad libitum throughout the studies. Water was also continuously available to all rats throughout the study.

d. Environment. Temperature and relative humidity in the housing area were maintained at 72 ± 6 °F, and 40 to 70 percent, respectively, with 12 hours of lighting each day.

e. Housing. Rats were housed individually in hanging stainless-steel cages measuring 40 cm high X 60 cm wide X 60 cm deep, equipped with bottled water and wire-lab block feeder.

f. 14-Day Study.

(1) A 14-day range finding study was conducted in male and female rats in accordance with the Toxicology Division standing operating procedure (SOP) for 14- and 90-Day Feeding Studies (reference 7).

(2) Forty-eight male and forty-eight female Sprague Dawley, Caesarean-derived, Barrier Restrained rats 6 to 8 weeks old were purchased from Charles River Laboratories of Wilmington, Massachusetts. Following a 1-week acclimation period, animals were randomly distributed into eight dosage groups of six rats, each sex. Daily dosage levels were set at 0, 25, 50, 100, 200, 400, 800, and 1,600 mg/kg/day. Animals were dosed by gavage on a 7 day per week basis, with a staggered start between males and females to accommodate terminal necropsies.

(3) A fresh 100 mg/ml working suspension of TCM in distilled water was made daily. The suspension was randomly sampled and independently verified for content by free chlorine analysis. Daily doses were calculated automatically by computer and reflected updated body weight values as they occurred.

(4) Body weights and food consumption were measured and recorded on days 0, 1, 3, 7, and 14. Animals were observed daily for toxic signs. Water consumption was not monitored during this study.

(5) Prior to necropsy on the final day of test, blood samples were collected by intracardiac puncture from all study rats. Clinical chemistry and hematology values were determined from all valid samples. The Table lists the clinical tests performed on the blood samples taken.

(6) Following the 14-day study period, surviving rats were sacrificed by decapitation and necropsied. The brain, liver, kidneys, spleen, and testes/ovaries were removed and weighed. These weights were used for calculations of organ-to-brain and organ-to-body weight ratios. Vital organs were saved for possible histological examination.

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TABLE. CLINICAL TESTS

Clinical Chemistry	Hematology
Alkaline phosphatase	Hemoglobin
Glutamate oxalacetate transaminase (SGOT)	Hematocrit
Glutamate pyruvate transaminase (SGPT)	Erythrocyte count
Glutamyltranspeptidase (GGTP)	Leukocyte count
Glucose	Differential count
Calcium	Platelet count
Total bilirubin	
Blood urea nitrogen (BUN)	
Total protein	

g. 90-Day Study.

(1) A 90-day gavage study was conducted in rats in accordance with the Toxicology Division SOP for 14- and 90-day studies (reference 7).

(2) Rats were acclimated for a 1-week period, then randomly distributed into five groups of ten of each sex. Dose levels were set at 0, 30, 150, and 300 mg/kg/day, based on clinical chemistry effects seen in the range finding study. A vehicle control was also included in the study to determine the toxic effects, if any, of the addition of a surfactant.

(3) A fresh working suspension of 75 mg/mL TCM in distilled water was again made daily. Random samples were analyzed to verify the TCM concentrations of the working suspension. To keep the TCM suspended in the distilled water solution, constant stirring was required during compound administration. Due to foaming of the TCM during this procedure (observed during the 14-day study), a surfactant was added to diminish the effect. Triton X-100 (Octyl phenoxy polyethoxyethanol), distributed by Sigma Chemical Company, St. Louis, Missouri, was added to the working solution at a concentration of .08 percent. The vehicle control group received distilled water with a Triton X-100 concentration mimicking the TCM suspension.

(4) Animals were dosed every day for the 90-day duration, with a staggered start between sexes. Rats in the control and vehicle control group were given volumes based on the

300 mg/kg dosage level. Body weights were recorded for all rats once per week. Dosage volumes were recalculated automatically by the laboratory software when body weights were updated.

(5) Food and water were available ad libitum throughout the study. Food consumption was monitored on a Monday, Wednesday, and Friday basis during the study. Water consumption was not observed. Observations of toxic signs were made and recorded daily.

(6) Animals not surviving to term or determined to be moribund, were subjected to full necropsies at the time of death, unless autolysis had occurred. On the final day of testing, prior to necropsy, animals were bled by intracardiac puncture for clinical chemistry and hematology determinations.

(7) Rats surviving the 90-day duration were sacrificed by decapitation for necropsy. Following examination of external surfaces and internal cavities, major organs were removed, trimmed, and weighed for organ-to-body and organ-to-brain weight ratio calculations. Other organs and tissues collected and processed for microscopic examination (reference 8) included all gross lesions, brain, eye, pituitary, salivary gland, heart, thyroid, parathyroid, lungs, lymph node, trachea, esophagus, stomach, small and large intestines, adrenals, pancreas, liver, kidneys, urinary bladder, testes, prostate, ovaries, corpus and cervix uteri, skeletal muscle, and sections of sternebrae, vertebrae, and tibia-femoral joint with marrow.

6. RESULTS.

a. 14-Day Study.

(1) Verification of the TCM working solution by standard methods (Appendix B) showed the suspension to contain an average of 96.5 percent of the predicted concentration.

(2) Deaths occurred in 11 of 12 high dosage (1,600 mg/kg) male and female rats by day 3 of the study. The remaining female rat in this dosage group survived to term, becoming lethargic and emaciated. Two male rats from the 800 mg/kg group died after dosing on day 2, while a female rat of that same group died following dosing on day 9. Deaths in the 400 mg/kg dosage group occurred on day 9 and 10 for one male and one female rat, respectively (Appendix D). All other rats survived the 14-day dosing regimen with varying degrees of toxic signs, i.e., ruffled pelt, lethargy, diarrhea, emaciation, and labored breathing.

(3) Analysis of variance using Duncan's procedure showed female rats in the highest dosage group had lowered food consumption by day 1 of the study, and again on days 3-7, when compared to the control group. Male rats in the high dosage group exhibited lowered food consumption by day 1 with associated deaths of all by day 3. Male rats in the 800 mg/kg group also showed reduced consumption on day 1 but returned to normal consumption by day 3 and for the remainder of the study (Appendix E).

(4) Weight loss occurred in the two highest dosage groups (800 and 1,600 mg/kg) in both female and male rats by day 1 of the 14-day study (Appendix F). All remaining female rats in these groups recovered to normal consumption by day 3, but again experienced significant weight loss between days 3 to 7. The 800 mg/kg dosage group of male rats continued with weight loss through day 3 but reverted to normal gains for the remainder of the study. TCM did not significantly effect weight gains of the 25-400 mg/kg TCM groups.

(5) Significant decreases in clinical chemistry values were seen in both sexes of rats at 14 days when compared to their respective control groups. Compound related changes occurred in total bilirubin, total protein and BUN values beginning in the 100 mg/kg dose and continuing through the 1,600 mg/kg dosage group in female rats. Males showed decreases in SGOT levels in the 200-1,600 mg/kg doses, decreases in BUN values in the 50-1,600 mg/kg levels, decreases in total protein values in the 100-1,600 mg/kg dosages, and increases in blood glucose levels in the 200-1,600 mg/kg dose groups (Appendix G).

(6) No significant changes were seen in hematological parameters of TCM rats after 14 days, when compared to control group rats (Appendix H).

(7) Gross necropsy of both sexes of rats revealed lung changes consisting of mottled, raised areas associated with the physical oral administration of the compound and control. The frequency of these changes was common to all groups and no dose response relationship associated with compound administration could be established. Foaming of dosing solutions due to continuous stirring seemed to be contributing to some lung congestion and lung changes.

(8) Organs taken at necropsy showed no significant differences in weight when TCM groups were compared with control organ weights (Appendix I). An analysis of organ-to-body weight ratios and organ-to-brain weight ratios also revealed no significant difference between controls and TCM groups.

b. 90-Day Study.

(1) Analysis of random samples taken from the TCM working suspension during the study yielded an average recovery of 101 percent of the expected concentration.

(2) No significant effects were observed in the surfactant (Triton-X 100) control group, indicating its addition to the TCM solutions had no bearing on the outcome of the study.

(3) Weekly food consumption figures for the 90-day study are displayed in Appendix J. Female rats in the high dosage group showed significantly lower food consumption (when compared to that of the control group) during the eighth week, but returned to normal the following week. No significant depression in food consumption was seen with male rats.

(4) Appendix K shows graphic representations of weight gains (loses) for both male and female rats. Significant weight loses were experienced during weeks 7 and 11 in female and male rats respectively. Both sexes returned to nonsignificant weight gains (loses) for the remainder of the study.

(5) Blood taken prior to necropsy at 90 days revealed only minor significant changes in clinical chemistry values (Appendix L). Female rats in the 150 and 300 mg/kg dosage groups showed a decrease in calcium content, while male rats had decreased total protein values in the high-dose group and elevated sugar levels in the 150 mg/kg group. No trends could be established related to compound administration.

(6) Examination of 90-day hematology values showed a significant decrease in the number of red blood cells in the 300 mg/kg male rats (Appendix M). No other significance was noted and again changes could not be directly related to TCM administration.

(7) Appendix N lists 90-day organ weights, organ-to-body weight ratios, and organ-to-brain weight ratios. Liver weights of female rats in the 300 mg/kg dosage group showed a significant increase when taken as a percentage of their body weight.

(8) Gross necropsies of animals in the 300 mg/kg and 150 mg/kg dosage groups, dying during the study, showed hemorrhagic erosion of the stomach mucosa as well as stomach and intestinal distention. Lungs from these rats exhibited varying degrees of congestion with white spotting. Rats surviving to term necropsy showed similar incidental signs across all groups with no dose response patterns being established.

(9) The majority of nonsurviving rats were found to have congestion of multiple organs (adrenal glands, brain, kidneys, liver, lung and pituitary) following histopathologic evaluation. This condition consisted of engorgement of the small blood vessels with blood. One male and female rat from the high dosage group had suppurative tracheitis which consisted of neutrophilic infiltration in the wall of the trachea, with accumulation of inflammatory cells and debris in the trachea lumen. This unusual lesion was considered to be associated with compound administration, despite the overall low incidence rate.

(10) Histopathologic examination of tissues and organs taken at necropsy revealed a low incidence of lesions in the nonglandular region of the stomach of male and female rats from the 300 mg/kg group (reference 9). Similar hyperplasia was noted in one male rat from the 150 mg/kg group. Chronic inflammation of the stomach consisted of a mixed inflammatory cell infiltration and a variable degree of inflammatory edema. Hyperplasia of the nonglandular epithelium consisted of thickening and irregularity of epithelial lining. These lesions were graded as mild or moderate and were considered to be associated with compound administration.

7. DISCUSSION.

a. Necropsies of high dosage (300 mg/kg/day or greater) rats dying during the conduct of the 14- and 90-day studies showed deaths were associated with the physical aspects of oral administration of TCM. Irritation and erosion of the mucosal linings of the stomach and intestine as well as multiple organ congestion were common to animals not surviving to term. Surviving high dosage animals generally suffered from labored breathing, lethargy and diarrhea with resulting weight loss.

b. Histopathological examination of tissues and organs from the 90-day study also showed chronic inflammation of the stomach with edema and thickening of the epithelial lining. These mild to moderate lesions were seen in one 150 mg/kg/day rat and several at the 300 mg/kg/day level. One male and female rat from

the 300 mg/kg/day dosage group had suppurative tracheitis which was considered associated with compound administration, despite the overall low incidence.

c. Short term exposure to TCM caused significant blood chemistry changes seen in the 100-200 mg/kg/day TCM range, after 14 days. Surviving rats recovering from the initial insult and blood taken after the 90-day study showed little effect relating to chemistry values. Blood taken at 90-days from the 300 mg/kg/day male rats had a significant decrease in red blood cells, while hemoglobin and hematocrits for the same animals appear to be near significance when compared to other groups. This anemia is possibly linked to subchronic TCM exposure, although no clear dose response was established as conformation.

8. CONCLUSIONS. The conclusions from the 90-day study follow:

a. The no observed adverse effect level for oral administration of TCM to rats was 30 mg/kg/day.

b. The effect level for oral TCM administration to rats was 150 mg/kg/day, where moderate lesions were seen in the non-glandular epithelial lining of the stomach.

c. The subchronic oral administration of TCM in rats was associated with lesions in the stomach and trachea, while causing engorgement of the small blood vessels of the adrenal glands, brain, kidneys, liver, lung and pituitary as well as pulmonary edema. Red blood cell anemia was observed in high dosage male rats, which may have been associated with TCM exposure.

d. Trichloromelamine should be considered moderately toxic when ingested acutely, and continuous ingestion could cause serious health effects.

9. RECOMMENDATIONS.

a. Proceed with the use of TCM as a food service disinfectant. Use of TCM as directed will limit overexposure and resulting health effects.

b. Continue with recommended animal testing required to support the Army's registration for TCM usage with the EPA.

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APPENDIX A

REFERENCES

1. Technical Report, Study No. 75-51-0195-84, this Agency, subject: Preliminary Assessment of the Relative Toxicity of Candidate Disinfectant, Food Service (Chlorine-Iodine Type), NSN 6840-00-810-6396 and Trichloromelamine.

2. Technical Report, Study No. 75-51-0195-87, Hazelton Laboratories America, Inc., January 1987, subject: Mutagenicity of Trichloromelamine in a Mouse Lymphoma Mutation Assay.

3. Technical Report, Study No. 75-51-0668-86, Hazelton Laboratories America, Inc., December 1986, subject: Clastogenic Evaluation of Trichloromelamine in a In Vitro Cytogenic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells.

4. Technical Report, Study No. 75-51-0195-87, Hazelton Laboratories America, Inc., January 1987, subject: Evaluation of Trichloromelamine in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay.

5. Technical Report, Study No. 75-51-0668-87, Hazelton Laboratories America Inc., January 1987, subject: Mutagenicity Evaluation of Trichloromelamine, Lot #1933, Dorex, Inc., in the Ames Salmonella/Microsome Reverse Mutation Assay.

6. Technical Reports, Study Nos. 34811, 34812, 34813, Analytical Biochemistry Laboratories, August 1986, Acute Toxicity of Trichloromelamine to Bluegill Sunfish, Rainbow Trout, and Daphnia magna.

7. Standing Operating Procedure No. 63, USAEHA, Toxicology Division, December 1987, 14-Day Range Finding and 90-Day Feeding Study in Rats.

8. Standing Operating Procedure, Pathology Laboratory, Pathology and Animal Care Branch, Toxicology Division, Room 3201, Building E-2100.

9. Termination Pathology Report, Trichloromelamine: 90-Day Feeding Study in Rats, Study #40-0743-88, George A. Parker, D.V.M., Ltd, 27 July 1989.

APPENDIX B

VERIFICATION OF TCM BY STANDARD METHODS

408 A. Iodometric Method I

1. General Discussion

a. Principle: Chlorine will liberate free iodine from potassium iodide (KI) solutions at pH 8 or less. The liberated iodine is titrated with a standard solution of sodium thiosulfate ($Na_2S_2O_3$) with starch as the indicator. Titrate at pH 3 to 4 because the reaction is not stoichiometric at neutral pH due to partial oxidation of thiosulfate to sulfate.

b. Interference: Oxidized forms of manganese and other oxidizing agents interfere. Reducing agents such as organic sulfides also interfere. Although the neutral titration minimizes the interfering effect of ferric and nitrite ions, the acid titration is preferred because some forms of combined chlorine do not react at pH 7. Use only acetic acid for the acid titration; sulfuric acid (H_2SO_4) will increase interferences; *never use hydrochloric acid (HCl).* See Section 408.1 for discussion of other interferences.

c. Minimum detectable concentration: The minimum detectable concentration approximates 40 μg Cl as Cl_2/L if 0.01*N* $Na_2S_2O_3$ is used with a 1000-mL sample. Concentrations below 1 mg/L cannot be determined accurately by the starch-iodide end point used in this method. Lower concentrations can be measured with the amperometric end point in Methods B and C.

2. Reagents

a. Acetic acid, conc (glacial).

b. Potassium iodide, KI, crystals.

c. Standard sodium thiosulfate, 0.1*N:* Dissolve 25 g $Na_2S_2O_3 \cdot 5H_2O$ in 1 L freshly boiled distilled water and standardize against potassium bi-iodate or potassium dichromate after at least 2 weeks storage. This initial storage is necessary to allow oxidation of any bisulfite ion present. Use boiled distilled water and add a few milliliters chloroform ($CHCl_3$) to minimize bacterial decomposition.

Standardize 0.1*N* $Na_2S_2O_3$ by one of the following:

1) Iodate method—Dissolve 3.249 g anhydrous potassium bi-iodate, $KH(IO_3)_2$, primary standard quality, or 3.567 g KIO_3 dried at 103 ± 2°C for 1 h, in distilled water and dilute to 1000 mL to yield a 0.1000*N* solution. Store in a glass-stoppered bottle.

To 80 mL distilled water, add, with constant stirring, 1 mL conc H_2SO_4, 10.00 mL 0.1000*N* $KH(IO_3)_2$, and 1 g KI. Titrate immediately with 0.1*N* $Na_2S_2O_3$ titrant until the yellow color of the liberated iodine almost is discharged. Add 1 mL starch indicator solution and continue titrating until the blue color disappears.

2) Dichromate method—Dissolve 4.904 g anhydrous potassium dichromate, $K_2Cr_2O_7$, of primary standard quality, in distilled water and dilute to 1000 mL to yield a 0.1000*N* solution. Store in a glass-stoppered bottle.

Proceed as in the iodate method, with the following exceptions: Substitute 10.00 mL 0.1000*N* $K_2Cr_2O_7$ for iodate and let reaction mixture stand 6 min in the dark before titrating with 0.1*N* $Na_2S_2O_3$ titrant.

$$\text{Normality } Na_2S_2O_3 = \frac{1}{\text{mL } Na_2S_2O_3 \text{ consumed}}$$

d. Standard sodium thiosulfate titrant, 0.01*N* or 0.025*N:* Improve the stability of 0.01*N* or 0.025*N* $Na_2S_2O_3$ by diluting an aged 0.1*N* solution, made as directed above, with freshly boiled distilled water. Add 4

g sodium borate and 10 mg mercuric iodide/L solution. For accurate work, standardize this solution daily in accordance with the directions given above, using 0.01*N* or 0.025*N* iodate or $K_2Cr_2O_7$. Use sufficient volumes of these standard solutions so that their final dilution is not greater than 1 + 4. To speed up operations where many samples must be titrated use an automatic buret of a type in which rubber does not come in contact with the solution. Standard titrants, 0.0100*N* and 0.0250*N*, are equivalent, respectively, to 354.5 μg and 886.3 μg Cl as Cl_2/1.00 mL.

e. Starch indicator solution: To 5 g starch (potato, arrowroot, or soluble), add a little cold water and grind in a mortar to a thin paste. Pour into 1 L of boiling distilled water, stir, and let settle overnight. Use clear supernate. Preserve with 1.25 g salicylic acid, 4 g zinc chloride, or a combination of 4 g sodium propionate and 2 g sodium azide/L starch solution. Some commercial starch substitutes are satisfactory.

f. Standard iodine, 0.1*N:* See 408B.3*g*.

g. Dilute standard iodine, 0.0282*N:* See 408B.3*h*.

3. Procedure

a. Volume of sample: Select a sample volume that will require no more than 20 mL 0.01*N* $Na_2S_2O_3$ and no less than 0.2 mL for the starch-iodide end point. For a chlorine range of 1 to 10 mg/L, use a 500-mL sample; above 10 mg/L, use proportionately less sample. Use smaller samples and volumes of titrant with the amperometric end point.

b. Preparation for titration: Place 5 mL acetic acid, or enough to reduce the pH to between 3.0 and 4.0, in a flask or white porcelain casserole. Add about 1 g KI estimated on a spatula. Pour sample in and mix with a stirring rod.

c. Titration: Titrate away from direct sunlight. Add 0.025*N* or 0.01*N* $Na_2S_2O_3$ from a buret until the yellow color of the liberated iodine almost is discharged. Add 1 mL starch solution and titrate until blue color is discharged.

If the titration is made with 0.025*N* $Na_2S_2O_3$ instead of 0.01*N*, then, with a 1-L sample, 1 drop is equivalent to about 50 μg/L. It is not possible to discern the end point with greater accuracy.

d. Blank titration: Correct result of sample titration by determining blank contributed by oxidizing or reducing reagent impurities. The blank also compensates for the concentration of iodine bound to starch at the end point.

Take a volume of distilled water corresponding to the sample used for titration in ¶s 3*a-c*, add 5 mL acetic acid, 1 g KI, and 1 mL starch solution. Perform blank titration as in 1) or 2) below, whichever applies.

1) If a blue color develops, titrate with 0.01*N* or 0.025*N* $Na_2S_2O_3$ to disappearance of blue color and record result.

2) If no blue color occurs, titrate with 0.0282*N* iodine solution until a blue color appears. Back-titrate with 0.01*N* or 0.025*N* $Na_2S_2O_3$ and record the difference.

Before calculating the chlorine concentration, subtract the blank titration of ¶ 1) from the sample titration; or, if necessary, add the net equivalent value of the blank titration of ¶ 2).

4. Calculation

For standardizing chlorine solution for temporary standards:

$$\text{mg Cl as } Cl_2/\text{mL} = \frac{(A \pm B) \times N \times 35.45}{\text{mL sample}}$$

For determining total available residual chlorine in a water sample:

$$\text{mg Cl as } Cl_2/\text{L} = \frac{(A \pm B) \times N \times 35\,450}{\text{mL sample}}$$

where:

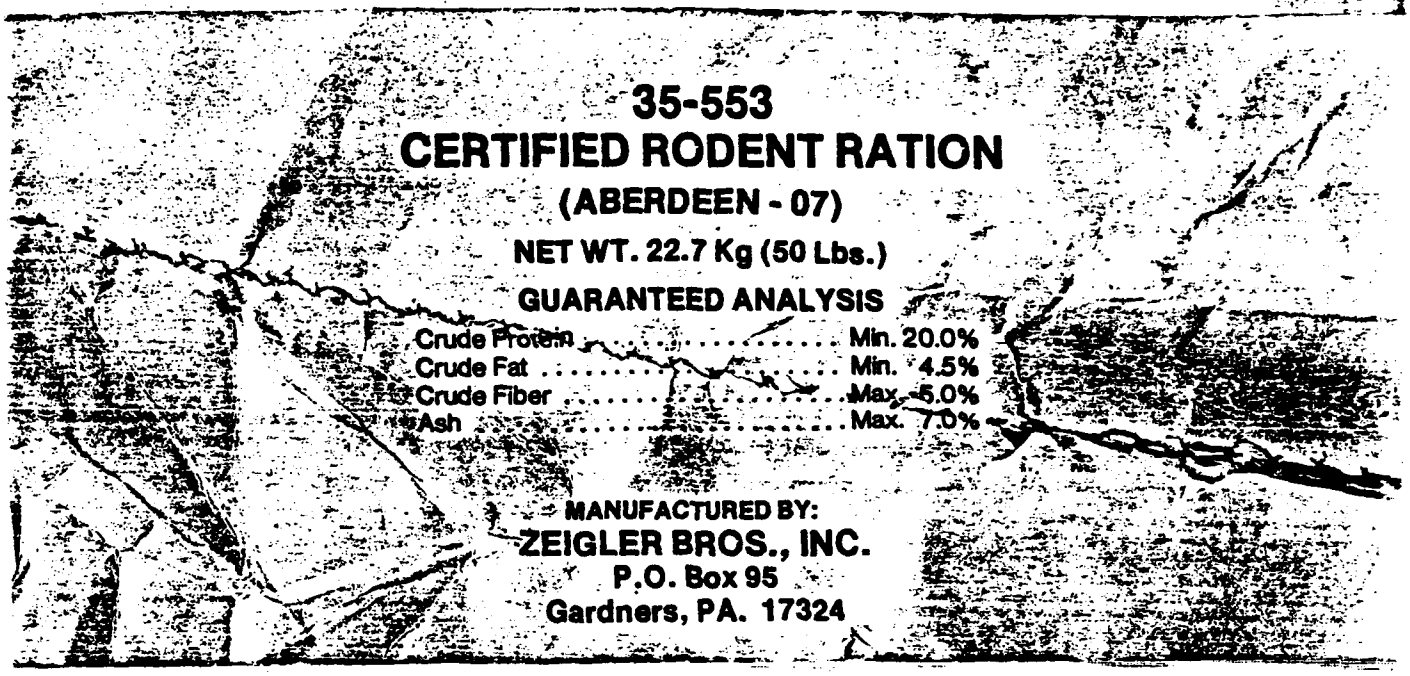
A = mL titration for sample,
B = mL titration for blank (positive or negative), and
N = normality of $Na_2S_2O_3$.

5. Precision and Accuracy

References 1 and 2 give the results of nine methods used to analyze synthetic water samples without interferences; variations of five of the methods appear in this edition. More current data are not now available.

APPENDIX C

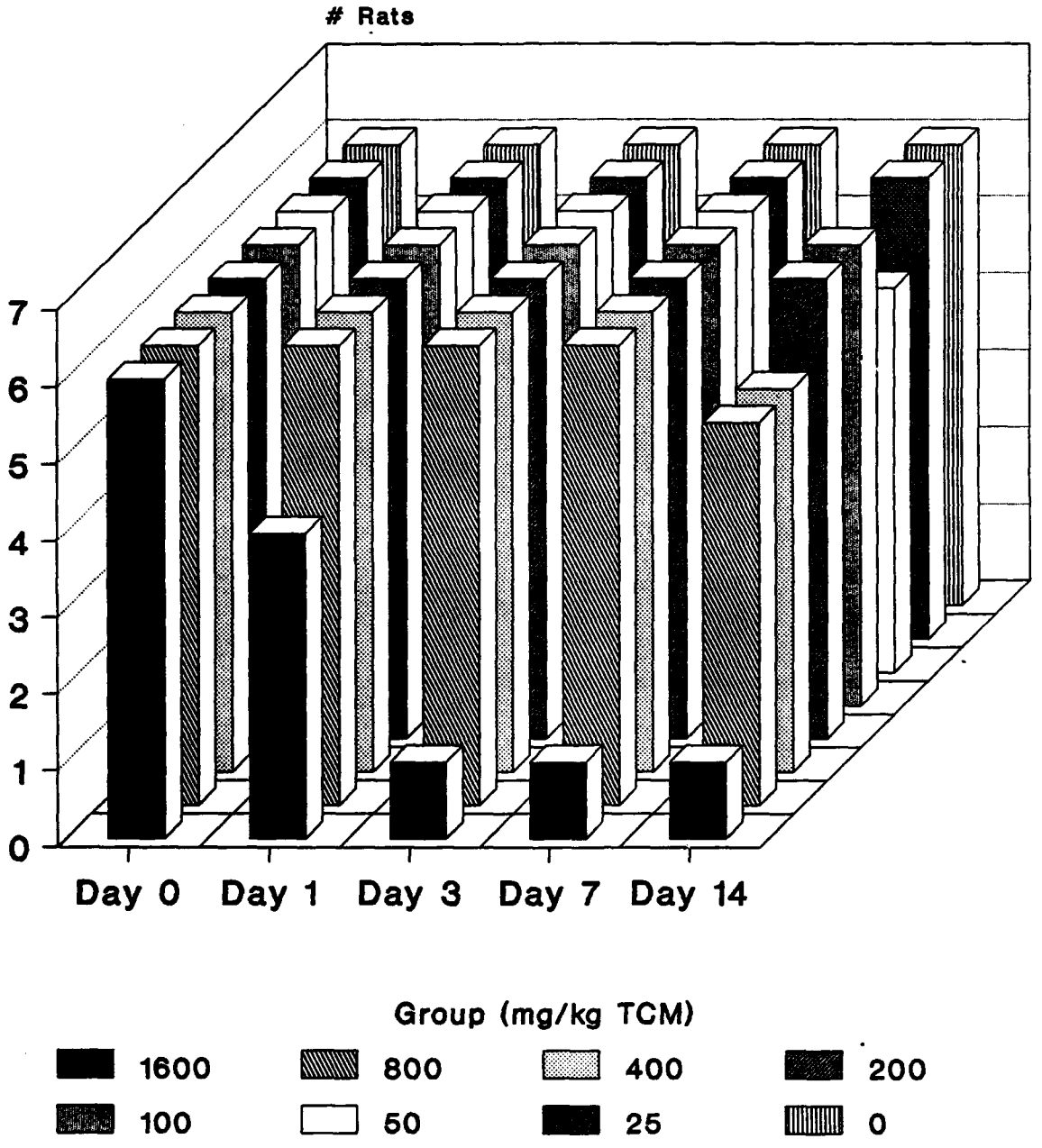
CERTIFIED RODENT RATION


35-553
CERTIFIED RODENT RATION
(ABERDEEN - 07)
NET WT. 22.7 Kg (50 Lbs.)
GUARANTEED ANALYSIS
Crude Protein ..... Min. 20.0%
Crude Fat ..... Min. 4.5%
Crude Fiber ..... Max. 5.0%
Ash ..... Max. 7.0%
MANUFACTURED BY:
ZEIGLER BROS., INC.
P.O. Box 95
Gardners, PA. 17324

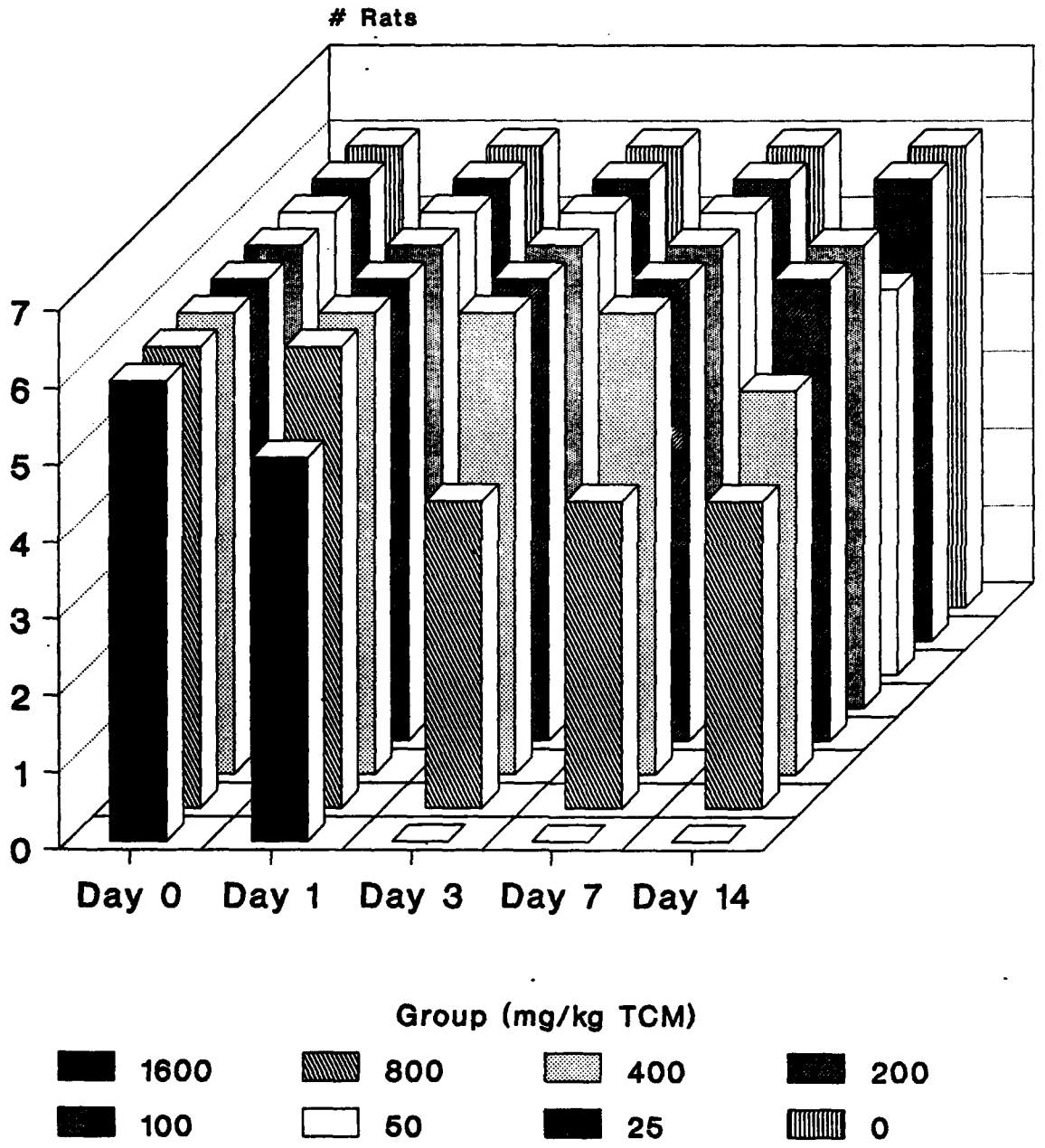
APPENDIX D

14-DAY SURVIVABILITY OF MALE AND FEMALE RATS

14-DAY TCM STUDY #75-51-0743-88
SURVIVABILITY - FEMALE RATS



14-DAY TCM STUDY #75-51-0743-88
SURVIVABILITY - MALE RATS



APPENDIX E

14-DAY FOOD CONSUMPTION OF MALE AND FEMALE RATS

14-DAY TCM STUDY NO. 75-51-0743-88(2)
SUMMARY OF FOOD CONSUMPTION (GRAMS)
FEMALE RATS

Period	Group	1 Control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg
Day 0-1	MEAN	20.8	20.3	21.2	21.2	19.5	20.3	13.8	6.8*
	S.D.	1.6	3.0	2.1	3.3	3.0	3.7	5.5	3.1
	N	6	6	6	6	6	6	6	4
Day 1-3	MEAN	43.2	41.2	44.5	40.2	35.8	40.3	35.0	30.0
	S.D.	4.0	3.6	3.9	3.5	13.0	7.1	12.6	-
	N	6	6	6	6	6	6	6	1
Day 3-7	MEAN	85.7	80.7	87.5	79.5	82.8	73.7	64.8	46.0*
	S.D.	10.0	11.0	8.7	4.1	6.6	14.7	14.5	-
	N	6	6	6	6	6	6	6	1
Day 7-14	MEAN	151.5	142.3	149.0	140.2	150.8	132.0	133.3	140.0
	S.D.	13.1	17.5	27.3	9.5	9.8	23.2	18.7	-
	N	6	6	5	6	6	5	5	1

* Indicates significance at the 0.05 level.

14-DAY TCM STUDY NO. 75-51-0743-88(2)
SUMMARY OF FOOD CONSUMPTION (GRAMS)
MALE RATS

Period	Group	1 Control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg
Day 0-1	MEAN	28.7	27.2	28.5	28.5	26.0	27.7	14.8*	6.2*
	S.D.	2.0	5.9	3.6	3.1	5.1	2.7	11.3	6.5
	N	6	6	6	6	6	6	6	5
Day 1-3	MEAN	54.5	41.0	53.8	54.0	64.3	49.0	28.0	-
	S.D.	5.3	22.1	5.3	3.5	12.5	18.9	14.9	-
	N	6	6	6	6	6	6	4	0
Day 3-7	MEAN	113.7	103.7	111.2	115.3	101.2	114.0	103.0	-
	S.D.	9.6	22.0	5.3	7.4	17.6	14.6	4.7	-
	N	6	6	6	6	6	6	6	0
Day 7-14	MEAN	207.5	210.8	196.2	210.3	193.3	209.6	178.3	-
	S.D.	27.8	15.9	17.5	18.6	22.7	42.5	19.9	-
	N	6	6	6	6	6	5	4	0

* Indicates significance at the 0.05 level.

APPENDIX F

14-DAY WEIGHT GAINS/LOSS OF MALE AND FEMALE RATS

14-DAY TCM STUDY NO. 75-51-0743-88(2)
SUMMARY OF WEIGHT GAINS (GRAMS)
FEMALE RATS

Period	Group	1 Control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg
Days 0-1	MEAN	5.3	4.0	5.0	4.5	2.2	2.5	-1.8*	-11.5*
	S.D.	1.4	2.4	3.5	2.8	4.7	5.0	5.5	6.95
	N	6	6	6	6	6	6	6	4
Day 1-3	MEAN	6.8	5.7	6.3	7.2	2.7	4.7	6.2	6.0
	S.D.	4.6	1.8	3.6	2.0	8.7	6.9	6.2	0.0
	N	6	6	6	6	6	6	6	1
Day 3-7	MEAN	11.7	10.2	13.2	10.0	11.8	0.5	-5.3*	-20.0*
	S.D.	4.2	3.1	2.5	3.6	4.1	16.3	17.8	0.0
	N	6	6	6	6	6	6	6	1
Day 7-14	MEAN	23.5	21.0	25.4	19.2	29.2	23.0	24.2	44.0
	S.D.	6.6	3.3	7.1	5.5	4.7	9.8	22.3	0.0
	N	6	6	5	6	6	5	5	1
Total Gain	MEAN	47.3	40.8	59.4	40.8	45.8	28.8	23.2*	24.0
	S.D.	6.3	7.4	10.5	6.1	12.6	13.1	21.1	0.0
	N	6	6	5	6	6	5	5	1

* Indicates significance at the 0.05 level.

14-DAY TCM STUDY NO. 75-51-0743-88(2)
SUMMARY OF WEIGHT GAINS (GRAMS)
MALE RATS

Period	Group	1 Control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg
Day 0-1	MEAN	9.3	3.2	8.5	7.2	6.8	6.0	-7.3*	-16.2*
	S.D.	2.1	10.4	2.8	2.2	3.6	1.7	14.0	11.3
	N	6	6	6	6	6	6	6	5
Day 1-3	MEAN	11.7	1.3	12.0	14.5	6.5	7.3	-8.0*	-
	S.D.	3.6	21.0	2.9	1.4	14.3	18.4	15.8	-
	N	6	6	6	6	6	6	4	0
Day 3-7	MEAN	33.5	34.3	30.0	30.5	26.3	33.5	28.8	-
	S.D.	5.1	6.1	2.5	3.9	11.5	6.9	9.3	-
	N	6	6	6	6	6	6	4	0
Day 7-14	MEAN	50.5	55.0	44.7	52.7	51.5	51.6	42.3	-
	S.D.	10.1	9.2	13.0	4.6	6.8	11.4	13.5	-
	N	6	6	6	6	6	5	4	0
Total Gain	MEAN	105.0	93.8	95.2	104.8	91.2	98.2	67.5	-
	S.D.	17.3	22.9	13.2	9.1	18.8	33.4	27.2	-
	N	6	6	6	6	6	5	4	0

* Indicates significance at the 0.05 level.

APPENDIX G

14-DAY CLINICAL CHEMISTRY SUMMARY OF MALE AND FEMALE RATS

14-DAY TCM STUDY NO. 75-51-0743-88(2)
CLINICAL CHEMISTRY SUMMARY
FEMALE RATS

Test	Group	1 Control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg
ALK. PHOS.	MEAN	330.6	463.2	336.5	396.7	420.7	262.5	265.8	205.0
IU/L	S.D.	226.3	100.8	84.7	172.1	131.3	51.4	40.9	-
	N	6	6	6	4	5	5	3	1
SGOT	MEAN	117.2	103.1	86.7	88.5	78.8	70.4	63.7	132.3
IU/L	S.D.	37.2	10.4	15.4	6.5	55.7	10.3	9.4	-
	N	6	6	6	4	5	5	3	1
SGPT	MEAN	34.8	37.1	38.6	38.9	36.4	35.1	38.3	41.5
IU/L	S.D.	7.7	3.1	7.8	10.4	3.3	4.9	11.8	-
	N	6	6	6	4	5	5	3	1
GLUCOSE	MEAN	144.2	152.6	140.5	135.9	147.7	152.0	148.7	181.4
IU/L	S.D.	23.6	25.2	19.6	11.1	9.3	7.0	8.4	-
	N	6	6	6	4	5	5	3	1
TOT. BILI.	MEAN	0.6	0.5	0.5	0.5*	0.4*	0.3*	0.4*	0.3*
MG/DL	S.D.	0.1	0.1	0.1	0.1	0.1	0.1	0.1	-
	N	6	6	6	4	5	5	3	1
BUN	MEAN	25.8	25.5	26.9	24.1*	21.2*	18.3*	17.7*	17.6
MG/DL	S.D.	1.6	1.2	4.4	3.0	2.4	3.0	4.9	-
	N	6	6	6	4	5	5	3	1
TOT. PROT.	MEAN	7.2	7.3	7.2	7.3*	7.1*	6.3*	6.0	6.0
G/DL	S.D.	0.5	0.5	0.4	0.8	0.6	0.2	0.3	-
	N	6	6	6	4	5	5	3	1
CALCIUM	MEAN	9.0	10.6	10.4	10.2	10.5	10.7	10.5	12.5
MG/DL	S.D.	4.0	0.7	0.7	0.4	0.4	0.5	0.5	-
	N	6	6	6	4	5	5	3	1

* Indicates significance at the 0.05 level.

ALK. PHOS. - Alkaline Phosphatase
SGOT - Serum Glutamic Oxaloacetic Transaminase
SGPT - Serum Glutamic Pyruvic Transaminase
TOT. BILI. - Total Bilirubin
BUN - Blood Urea Nitrogen
TOT. PROT. - Total Protein

14-DAY TCM STUDY NO. 75-51-0743-88(2)
CLINICAL CHEMISTRY SUMMARY
MALE RATS

Test	Group	1 Control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg
ALK. PHOS.	MEAN	619.3	590.4	639.2	647.6	557.6	417.1	481.6	-
IU/L	S.D.	204.4	194.6	224.2	142.6	144.7	147.6	203.6	-
	N	6	6	6	6	6	5	4	-
SGOT	MEAN	121.0	118.2	113.1	117.5	85.5*	85.5*	75.4*	-
IU/L	S.D.	23.2	11.9	13.2	16.4	8.2	20.8	7.9	-
	N	6	6	6	6	6	5	4	-
SGPT	MEAN	46.7	42.9	43.9	46.2	40.0	38.3	39.2	-
IU/L	S.D.	12.7	5.0	2.8	5.4	5.0	11.9	7.6	-
	N	6	6	6	6	6	5	4	-
GLUCOSE	MEAN	119.8	135.0	129.7	126.4	158.5*	151.1*	171.9*	-
IU/L	S.D.	9.5	47.3	13.2	7.6	25.8	4.2	7.9	-
	N	6	6	6	6	6	5	4	-
TOT. BILI.	MEAN	0.5	0.4	0.4	0.5	0.4	0.4	0.4	-
MG/DL	S.D.	0.1	0.1	0.1	0.1	0.1	0.1	0.1	-
	N	6	6	6	6	6	5	4	-
BUN	MEAN	25.9	23.4	22.6*	22.2*	16.3*	17.6*	16.6*	-
MG/DL	S.D.	1.7	3.4	1.1	2.0	2.6	2.1	3.0	-
	N	6	6	6	6	6	5	4	-
TOT. PROT.	MEAN	7.3	6.8	6.7	6.8*	6.4*	6.1*	6.2*	-
G/DL	S.D.	0.6	0.4	0.3	0.6	0.2	0.4	0.2	-
	N	6	6	6	6	6	5	4	-
CALCIUM	MEAN	10.4	10.6	10.4	10.4	10.6	10.3	10.5	-
MG/DL	S.D.	0.5	1.0	0.6	0.6	0.8	0.4	0.4	-
	N	6	6	6	6	6	5	4	-

* Indicates significance at the 0.05 level.

ALK. PHOS. - Alkaline Phosphatase
SGOT - Serum Glutamic Oxaloacetic Transaminase
SGPT - Serum Glutamic Pyruvic Transaminase
TOT. BILI. - Total Bilirubin
BUN - Blood Urea Nitrogen
TOT. PROT. - Total Protein

APPENDIX H

14-DAY HEMATOLOGY VALUES OF MALE AND FEMALE RATS

ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - HEMOGLOBIN (g/dl)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg	9	10	GRAND TOTALS	SUM OF SQUARES
771	759	767	764	760	781	761	793	.		* 15.2	13.4	15.0	14.5	15.3	14.4	18.2	13.6				1803.50
779	763	778	766	769	782	770				* 15.2	14.5	14.6	14.5	14.9	14.9	13.8					1499.16
787	791	783	768	784	794	773				* 15.1	14.8	15.3	15.5	14.3	14.9	15.1					1575.90
790	795	786	774	789	797	775				* 14.4	16.0	14.0	NS	14.7	14.1	14.0					1270.26
796	798	799	780	792	801	788				* 14.5	15.0	15.4	14.4	NS	15.3	13.9					1307.07
802	803	806	809	808						* NS	14.1	15.0	NS	15.5							664.06
										Totals	74.40	87.80	89.30	58.90	74.70	73.60	75.00	13.60	0.00	0.00	547.30	8119.95
										Observation	5.00	6.00	6.00	4.00	5.00	5.00	5.00	1.00	1.00	1.00	37.00	
										Mean	14.88	14.63	14.88	14.73	14.94	14.72	15.00	13.60	0.00	0.00	14.79	
										Std Dev	0.35	0.80	0.47	0.45	0.43	0.42	1.67	ERR	ERR	ERR		
										# of Group	8							NS = INSUFFICIENT SAMPLE				

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	2.03	7	0.29	0.38
Within Groups	22.32	29	0.77	
Totals	24.35	36		

F-table Lookup (num. 7,denom. 29)
F RATIO .05 = 2.35
F RATIO .01 = 3.33

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - HEMOGLOBIN (g/dl)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg	9	10	GRAND TOTALS	SUM OF SQUARES
823	811	812	816	813	815	827				* 15.1	14.0	14.5	14.6	14.4	14.1	14.6					1466.75
826	822	831	841	834	825	835				* 14.9	15.3	15.6	15.5	14.9	NS	13.3					1338.61
829	824	836	842	837	844	851				* 14.8	14.3	13.8	14.8	14.8	14.9	13.3					1450.95
838	845	839	850	846	853	858				* 14.8	14.8	14.5	15.1	15.6	14.7	14.8					1554.83
848	854	843	852	849	857					* 14.4	15.7	15.6	13.9	15.1	16.0						1374.43
863	817	862	855	861						* 14.4	14.0	14.8	15.2	14.4	15.0						1285.80
										Totals	88.40	88.10	88.80	89.10	89.20	74.70	56.00	0.00	0.00	0.00	574.30	8471.37
										Observation	6.00	6.00	6.00	6.00	6.00	5.00	4.00	1.00	1.00	1.00	39.00	
										Mean	14.73	14.68	14.80	14.85	14.87	14.94	14.00	0.00	0.00	0.00	14.73	
										Std Dev	0.26	0.65	0.64	0.51	0.41	0.62	0.70	ERR	ERR	ERR		
										# of Group	7							NS = INSUFFICIENT SAMPLE				

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	2.59	6	0.43	1.17
Within Groups	11.84	32	0.37	
Totals	14.43	38		

F-table Lookup (num. 6,denom. 32)
F RATIO .05 = 2.40
F RATIO .01 = 3.42

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - HEMATOCRIT (%)

ANIMAL # GROUPS 1	2	3	4	5	6	7	8	9	10	*DATA GROUPS	1 control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg	9	10	GRAND TOTALS	SUM OF SQUARES
771	759	767	764	760	781	761	793			*	40.5	36.2	42.6	40.2	40.6	39.2	47.0	36.6				13115.05
779	763	778	766	769	782	770				*	41.0	38.1	38.6	38.5	40.8	41.0	37.7					10871.75
787	791	783	768	784	794	773				*	41.6	40.5	40.5	41.9	38.5	40.3	39.1					11401.82
790	795	786	774	789	797	775				*	41.1	43.7	37.3	NS	39.5	38.3	40.6					9665.69
796	798	799	780	792	801	788				*	39.2	41.3	41.5	38.2	NS	41.3	37.6					9543.27
802	803	806	809	808						*	NS	37.8	41.6	NS	42.4							4957.16
										Totals	203.40	237.60	242.10	158.80	201.80	200.10	202.00	36.60	0.00	0.00	1482.40	59554.74
										Observation	5.00	6.00	6.00	4.00	5.00	5.00	5.00	1.00	1.00	1.00	37.00	
										Mean	40.68	39.60	40.35	39.70	40.36	40.02	40.40	36.60	0.00	0.00	40.06	
										Std Dev	0.82	2.50	1.84	1.48	1.31	1.12	3.48	0.00	ERR	ERR		
										# of Group	8							NS = INSUFFICIENT SAMPLE				

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	17.22	7	2.46	0.49
Within Groups	145.36	29	5.01	
Totals	162.58	36		

F-table Lookup (num. 7,denom. 29)
F RATIO .05 = 2.35
F RATIO .01 = 3.33

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - HEMATOCRIT (%)

ANIMAL # GROUPS 1	2	3	4	5	6	7	8	9	10	*DATA GROUPS 1 control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg	9	10	GRAND TOTALS	SUM OF SQUARES
823	811	812	816	813	815	827				42.0	40.3	41.8	40.2	40.5	39.1	39.9					11512.44
826	822	831	841	834	825	835				42.5	44.1	42.9	42.3	40.8	NS	36.3					10363.09
829	824	836	842	837	844	851				41.8	39.6	38.7	41.9	40.8	42.5	35.0					11264.59
838	845	839	850	846	853	858				39.6	41.2	39.4	41.6	43.2	40.3	40.5					11679.10
848	854	843	852	849	857					40.0	43.9	42.8	38.1	41.2	42.1						10280.51
863	817	862	855	861						39.0	40.5	39.1	39.4	38.6	40.3						9356.47
										Totals	244.90	249.60	244.70	243.50	245.10	204.30	151.70	0.00	0.00	0.00	1583.80	64456.20
										Observation	6.00	6.00	6.00	6.00	6.00	5.00	4.00	1.00	1.00	1.00	39.00	
										Mean	40.82	41.60	40.78	40.58	40.85	40.86	37.93	0.00	0.00	0.00	40.61	
										Std Dev	1.33	1.76	1.76	1.50	1.34	1.26	2.33	ERR	ERR	ERR		
										# of Group	7											

NS = INSUFFICIENT SAMPLE

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	35.82	6	5.97	1.88
Within Groups	101.86	32	3.18	
Totals	137.68	38		

F-table Lookup (num. 6,denom. 32)
F RATIO .05 = 2.40
F RATIO .01 = 3.42

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - RED BLOOD CELLS (10E+6/μL)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg	9	10	GRAND TOTALS	SUM OF SQUARES
771	759	767	764	760	781	761	793			* 6.59	5.94	6.67	6.66	6.56	6.25	7.83	5.89				345.78
779	763	778	766	769	782	770				* 6.84	6.36	6.37	6.39	6.76	6.55	6.17					295.31
787	791	783	768	784	794	773				* 6.86	6.66	6.55	6.72	6.29	5.51	6.59					292.83
790	795	786	774	789	797	775				* 6.62	6.98	6.18	NS	6.62	6.40	6.75					261.08
796	798	799	780	792	801	788				* 6.51	6.47	6.89	6.44	NS	6.59	6.10					253.82
802	803	806	809	808						* NS	6.44	6.54	NS	6.94							132.41
										Totals	33.42	38.85	39.20	26.21	33.17	31.31	33.44	5.89	0.00	0.00	241.49	1581.24
										Observation	5.00	6.00	6.00	4.00	5.00	5.00	5.00	1.00	1.00	1.00	37.00	
										Mean	6.68	6.48	6.53	6.55	6.63	6.26	6.69	5.89	0.00	0.00	6.53	
										Std Dev	0.14	0.31	0.22	0.14	0.22	0.39	0.62	0.00	ERR	ERR		
										# of Group	8				NS = INSUFFICIENT SAMPLE						

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	1.09	7	0.16	1.12
Within Groups	4.01	29	0.14	
Totals	5.09	36		

F-table Lookup (num. 7,denom. 29)
F RATIO .05 = 2.35
F RATIO .01 = 3.33

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - RED BLOOD CELLS (10E+6/μL)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg	9	10	GRAND TOTALS	SUM OF SQUARES
823	811	812	816	813	815	827				* 6.78	6.30	6.63	6.55	6.21	6.33	6.63					295.11
826	822	831	841	834	825	835				* 6.75	6.96	6.95	6.61	6.64	NS	5.96					265.61
829	824	836	842	837	844	851				* 6.61	6.41	6.21	6.49	6.56	6.45	5.61					281.57
838	845	839	850	846	853	858				* 6.59	6.57	6.43	6.62	6.94	6.27	6.29					298.80
848	854	843	852	849	857					* 6.27	6.82	7.00	5.94	6.81	6.66						260.84
863	817	862	855	861						* 6.14	6.33	6.37	6.47	6.10	6.27						236.73
										Totals 39.14	39.39	39.59	38.68	39.26	31.98	24.49	0.00	0.00	0.00	252.53	1638.66
										Observation 6.00	6.00	6.00	6.00	6.00	5.00	4.00	1.00	1.00	1.00	39.00	
										Mean 6.52	6.57	6.60	6.45	6.54	6.40	6.12	0.00	0.00	0.00	6.48	
										Std Dev 0.24	0.25	0.29	0.23	0.30	0.15	0.38	ERR	ERR	ERR		
										# of Group 7							NS = INSUFFICIENT SAMPLE				

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	0.71	6	0.12	1.37
Within Groups	2.78	32	0.09	
Totals	3.50	38		

F-table Lookup (num. 6,denom. 32)
F RATIO .05 = 2.40
F RATIO .01 = 3.42

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - MEAN CELL VOLUME (fL)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg	9	10	GRAND TOTALS	SUM OF SQUARES
771	759	767	764	760	781	761	793			* 61	60	63	60	61	62	59	61				29657.00
779	763	778	766	769	782	770				* 59	59	60	60	60	62	61					25327.00
787	791	783	768	784	794	773				* 60	60	61	61	61	62	59					25688.00
790	795	786	774	789	797	775				* 61	62	60	NS	59	59	61					21848.00
796	798	799	780	792	801	788				* 60	63	60	59	NS	62						18494.00
802	803	806	809	808						* NS	58	63	NS	60							10933.00
										Totals 301.00	362.00	367.00	240.00	301.00	307.00	240.00	61.00	0.00	0.00	2179.00	131947.00
										Observation 5.00	6.00	6.00	4.00	5.00	5.00	4.00	1.00	1.00	1.00	36.00	
										Mean 60.20	60.33	61.17	60.00	60.20	61.40	60.00	61.00	0.00	0.00	60.53	
										Std Dev 0.75	1.70	1.34	0.71	0.75	1.20	1.00	0.00	ERR	ERR		
										# of Group 8								NS = INSUFFICIENT SAMPLE			

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	10.01	7	1.43	0.85
Within Groups	46.97	28	1.68	
Totals	56.97	35		

F-table Lookup (num. 7,denom. 28)
F RATIO .05 = 2.35
F RATIO .01 = 3.33

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - MEAN CELL VOLUME (fL)

ANIMAL # GROUPS 1	2	3	4	5	6	7	8	9	10	*DATA * GROUPS	1 *control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg	9	10	GRAND TOTALS	SUM OF SQUARES
823	811	812	816	813	815	827				*	61	63	62	61	65	61	60					26801.00
826	822	831	841	834	825	835				*	62	63	61	63	61	NS	60					22824.00
829	824	836	842	837	844	851				*	63	61	62	64	61	65	62					27420.00
838	845	839	850	846	853	858				*	59	62	61	62	62	64	64					26926.00
848	854	843	852	849	857					*	63	63	60	64	60	63						23203.00
863	817	862	855	861						*	63	63	61	60	63	64						23324.00
										Totals	371.00	375.00	367.00	374.00	372.00	317.00	246.00	0.00	0.00	0.00	2422.00	150498.00
										Observation	6.00	6.00	6.00	6.00	6.00	5.00	4.00	1.00	1.00	1.00	39.00	
										Mean	61.83	62.50	61.17	62.33	62.00	63.40	61.50	0.00	0.00	0.00	62.10	
										Std Dev	1.46	0.76	0.69	1.49	1.63	1.36	1.66	ERR	ERR	ERR		
										# of Group	7							NS = INSUFFICIENT SAMPLE				

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	16.89	6	2.81	1.31
Within Groups	68.70	32	2.15	
Totals	85.59	38		

F-table Lookup (num. 6,denom. 32)
F RATIO .05 = 2.40
F RATIO .01 = 3.42

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - WHITE BLOOD CELLS (10E+3/μL)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg	9	10	GRAND TOTALS	SUM OF SQUARES
771	759	767	764	760	781	761	793			* 7.1	8.0	11.0	16.3	13.4	15.6	7.0	11.1				1096.23
779	763	778	766	769	782	770				* 3.6	7.5	11.5	11.7	5.4	7.2	5.6					450.71
787	791	783	768	784	794	773				* 9.6	7.3	7.5	8.0	6.8	11.8	9.4					539.54
790	795	786	774	789	797	775				* 7.4	8.2	6.0	NS	10.6	11.3	11.6					532.61
796	798	799	780	792	801	788				* 5.6	16.4	6.2	9.8	NS	11.1	7.3					611.30
802	803	806	809	808						* NS	8.7	10.9	NS	14.5							404.75
										Totals	33.30	56.10	53.10	45.80	50.70	57.00	40.90	11.10	0.00	0.00	348.00	3635.14
										Observation	5.00	6.00	6.00	4.00	5.00	5.00	5.00	1.00	1.00	1.00	37.00	
										Mean	6.66	9.35	8.85	11.45	10.14	11.40	8.18	11.10	0.00	0.00	9.41	
										Std Dev	1.99	3.19	2.34	3.09	3.56	2.67	2.10	0.00	ERR	ERR		
										# of Group	8				NS = INSUFFICIENT SAMPLE							

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ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	89.25	7	12.75	1.36
Within Groups	272.81	29	9.41	
Totals	362.06	36		

F-table Lookup (num. 7,denom. 29)
F RATIO .05 = 2.35
F RATIO .01 = 3.33

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - WHITE BLOOD CELLS (10E+3/μL)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg	9	10	GRAND TOTALS	SUM OF SQUARES
823	811	812	816	813	815	827				* 12.1	6.4	12.7	23.0	12.6	15.2	17.8					1584.30
826	822	831	841	834	825	835				* 11.1	13.3	13.6	15.1	8.3	NS	9.2					366.60
829	824	836	842	837	844	851				* 6.8	13.1	14.7	16.9	18.5	15.6	19.2					1673.80
838	845	839	850	846	853	858				* 6.2	14.9	11.9	13.1	10.9	13.8	16.7					1161.81
848	854	843	852	849	857					* 15.3	6.4	11.0	18.1	14.7	13.9						1132.96
863	817	862	855	861						* 20.6	10.4	15.3	10.7	14.8	12.2						1248.98
										Totals 72.10	64.50	79.20	96.90	79.80	70.70	62.90	0.00	0.00	0.00	526.10	7668.45
										Observation 6.00	6.00	6.00	6.00	6.00	5.00	4.00	1.00	1.00	1.00	39.00	
										Mean 12.02	10.75	13.20	16.15	13.30	14.14	15.73	0.00	0.00	0.00	13.49	
										Std Dev 4.94	3.35	1.51	3.90	3.23	1.20	3.87	ERR	ERR	ERR		
										# of Group 7					NS = INSUFFICIENT SAMPLE						

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	123.34	6	20.56	1.47
Within Groups	448.16	32	14.00	
Totals	571.50	38		

F-table Lookup (num. 6,denom. 32)
F RATIO .05 = 2.40
F RATIO .01 = 3.42

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

APPENDIX I

14-DAY SUMMARY OF ORGAN WEIGHTS

14-DAY TCM STUDY #75-51-0743-88(2)
SUMMARY OF ORGAN WEIGHTS (GRAMS)
MALE RATS

ORGAN	GROUP	1 Control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg
Body Weight	MEAN	302	293	295	305	285	303	262	---
	S.D.	25.0	28.2	16.9	18.3	30.8	38.6	17.3	---
	N	6	6	6	6	6	5	4	---
Brain	MEAN	1.90	1.86	1.84	1.86	1.78	1.81	1.76	---
	S.D.	0.067	0.118	0.063	0.129	0.027	0.062	0.057	---
	% BODY WT	0.631	0.639	0.624	0.610	0.632	0.605	0.677	---
	S.D.	0.053	0.047	0.034	0.050	0.065	0.073	0.061	---
	N	6	6	6	6	6	5	4	---
Adrenals	MEAN	0.067	0.065	0.060	0.063	0.059	0.061	0.060	---
	S.D.	0.011	0.007	0.002	0.006	0.009	0.008	0.010	---
	% BODY WT	0.022	0.022	0.020	0.021	0.021	0.020	0.023	---
	S.D.	0.002	0.002	0.001	0.003	0.002	0.002	0.005	---
	% BRAIN WT	3.52	3.50	3.26	3.40	3.29	3.36	3.38	---
	S.D.	0.5	0.3	0.2	0.4	0.5	0.4	0.5	---
	N	6	6	6	6	6	5	4	---
Kidneys	MEAN	2.69	2.74	2.53	2.59	2.43	2.65	2.42	---
	S.D.	0.277	0.221	0.295	0.167	0.184	0.253	0.278	---
	% BODY WT	0.891	0.940	0.856	0.850	0.856	0.879	0.925	---
	S.D.	0.057	0.067	0.063	0.018	0.063	0.067	0.090	---
	% BRAIN WT	141.94	147.28	137.51	139.90	136.17	146.21	137.24	---
	S.D.	13.7	6.5	12.9	10.3	10.7	14.9	16.1	---
	N	6	6	6	6	6	5	4	---
Testes	MEAN	2.79	2.99	2.85	2.78	2.77	2.70	2.39	---
	S.D.	0.212	0.284	0.113	0.317	0.196	0.173	0.490	---
	% BODY WT	0.926	1.025	0.969	0.914	0.981	0.899	0.925	---
	S.D.	0.068	0.093	0.065	0.105	0.122	0.098	0.232	---
	% BRAIN WT	147.31	160.43	155.32	150.17	155.31	148.89	135.20	---
	S.D.	13.3	9.6	6.9	16.1	11.4	11.4	23.4	---
	N	6	6	6	6	6	5	4	---
Liver	MEAN	15.64	14.52	14.19	14.99	12.98	14.80	13.24	---
	S.D.	2.823	1.636	1.509	2.324	1.653	3.414	1.716	---
	% BODY WT	5.142	4.957	4.799	4.915	4.546	4.829	5.049	---
	S.D.	0.560	0.232	0.295	0.682	0.169	0.592	0.355	---
	% BRAIN WT	822.82	779.08	772.59	813.82	727.14	814.61	753.15	---
	S.D.	139.3	69.1	86.5	161.5	89.7	179.3	114.4	---
	N	6	6	6	6	6	5	4	---

* Indicates significance at the 0.05 level.

14-DAY TCM STUDY #75-51-0743-88(2)
SUMMARY OF ORGAN WEIGHTS (GRAMS)
FEMALE RATS

ORGAN	GROUP	1 Control	2 25mg/kg	3 50mg/kg	4 100mg/kg	5 200mg/kg	6 400mg/kg	7 800mg/kg	8 1600mg/kg
Body Weight	MEAN	204	199	206	195	205	188	178	166
	S.D.	17.1	17.8	22.2	8.5	10.0	20.5	25.1	---
	N	6	6	6	6	6	5	5	1
Brain	MEAN	1.71	1.72	1.67	1.73	1.72	1.73	1.70	1.64
	S.D.	0.082	0.036	0.076	0.055	0.083	0.029	0.137	---
	% BODY WT	0.841	0.866	0.805	0.891	0.839	0.929	0.959	0.988
	S.D.	0.061	0.072	0.071	0.027	0.064	0.107	0.064	---
	N	6	6	6	6	6	5	5	1
Adrenals	MEAN	0.071	0.063	0.065	0.075	0.072	0.079	0.068	0.080
	S.D.	0.008	0.011	0.016	0.010	0.008	0.009	0.006	---
	% BODY WT	0.035	0.032	0.031	0.038	0.035	0.042	0.039	0.048
	S.D.	0.003	0.006	0.007	0.005	0.005	0.006	0.006	---
	% BRAIN WT	4.14	3.69	3.91	4.31	4.20	4.53	4.04	4.88
	S.D.	0.4	0.7	1.0	0.7	0.6	0.4	0.4	---
	N	6	6	6	6	6	5	5	1
Kidneys	MEAN	1.68	1.68	1.74	1.67	1.75	1.64	1.71	1.75
	S.D.	0.233	0.194	0.164	0.156	0.191	0.209	0.177	---
	% BODY WT	0.821	0.850	0.825	0.859	0.856	0.872	0.974	1.054
	S.D.	0.061	0.115	0.057	0.080	0.094	0.039	0.157	---
	% BRAIN WT	98.07	98.12	103.56	96.46	102.10	94.87	101.09	106.71
	S.D.	10.9	10.6	6.8	8.6	9.8	11.5	10.6	---
	N	6	6	6	6	6	5	5	1
Ovaries	MEAN	0.121	0.108	0.117	0.101	0.111	0.120	0.111	0.080
	S.D.	0.026	0.009	0.009	0.015	0.011	0.024	0.012	---
	% BODY WT	0.059	0.054	0.057	0.052	0.054	0.063	0.063	0.048
	S.D.	0.009	0.005	0.004	0.008	0.003	0.010	0.013	---
	% BRAIN WT	7.01	6.27	7.00	5.87	6.45	6.89	6.57	4.88
	S.D.	1.2	0.4	0.5	1.0	0.7	1.3	0.9	---
	N	6	6	6	6	6	5	5	1
Liver	MEAN	9.82	9.30	9.98	9.03	10.05	9.17	8.81	9.17
	S.D.	1.008	0.984	1.363	0.591	1.133	1.160	1.774	---
	% BODY WT	4.801	4.665	4.841	4.643	4.892	4.859	4.927	5.524
	S.D.	0.145	0.313	0.230	0.247	0.361	0.167	0.573	---
	% BRAIN WT	573.66	541.50	596.11	521.67	587.19	592.02	517.17	559.15
	S.D.	51.2	55.1	73.4	35.6	75.8	64.6	82.5	---
	N	6	6	6	6	6	5	5	1

* Indicates significance at the 0.05 level.

APPENDIX J

90-DAY FOOD CONSUMPTION OF MALE AND FEMALE RATS

90-DAY TCM STUDY #75-51-0743-88(2)
SUMMARY OF FOOD CONSUMPTION (GRAMS)
FEMALE RATS

WEEK	GROUP	1 Water	2 Triton-X	3 30mg/kg	4 150mg/kg	5 300mg/kg
1	MEAN	143	144	142	137	135
	S.D.	8.4	16.6	10.8	12.5	14.8
	N	10	10	10	10	9
2	MEAN	149	149	153	148	145
	S.D.	11.6	18.5	10.9	17.5	17.0
	N	10	10	10	10	9
3	MEAN	151	152	152	153	147
	S.D.	13.1	13.4	14.8	8.2	14.6
	N	10	10	10	10	8
4	MEAN	158	154	154	153	155
	S.D.	13.4	16.9	14.2	9.1	18.5
	N	10	10	10	10	7
5	MEAN	161	159	161	161	169
	S.D.	12.8	20.1	16.7	10.3	16.6
	N	10	10	10	10	7
6	MEAN	160	159	163	163	164
	S.D.	16.9	17.3	20.7	17.7	30.4
	N	10	10	10	10	7
7	MEAN	161	158	164	158	142
	S.D.	12.8	19.8	24.0	27.8	22.8
	N	10	10	10	10	7
8	MEAN	170	161	172	160	137*
	S.D.	13.4	16.3	23.1	25.9	37.9
	N	10	10	10	9	7
9	MEAN	160	158	155	163	149
	S.D.	13.0	20.1	14.8	19.2	25.6
	N	10	10	10	7	10
10	MEAN	165	162	164	160	153
	S.D.	18.6	20.4	24.6	19.6	21.4
	N	10	10	10	7	7
11	MEAN	167	164	164	159	148
	S.D.	11.3	19.0	31.2	17.2	37.7
	N	10	10	10	7	7
12	MEAN	150	151	148	149	131
	S.D.	11.3	15.6	27.9	14.7	33.8
	N	10	10	10	7	7
13	MEAN	155	144	147	145	134
	S.D.	15.7	15.1	25.4	19.0	21.2
	N	8	10	10	7	6

* Indicates significance at the 0.05 level.

90-DAY TCM STUDY #75-51-0743-88 (2)
SUMMARY OF FOOD CONSUMPTION (GRAMS)
MALE RATS

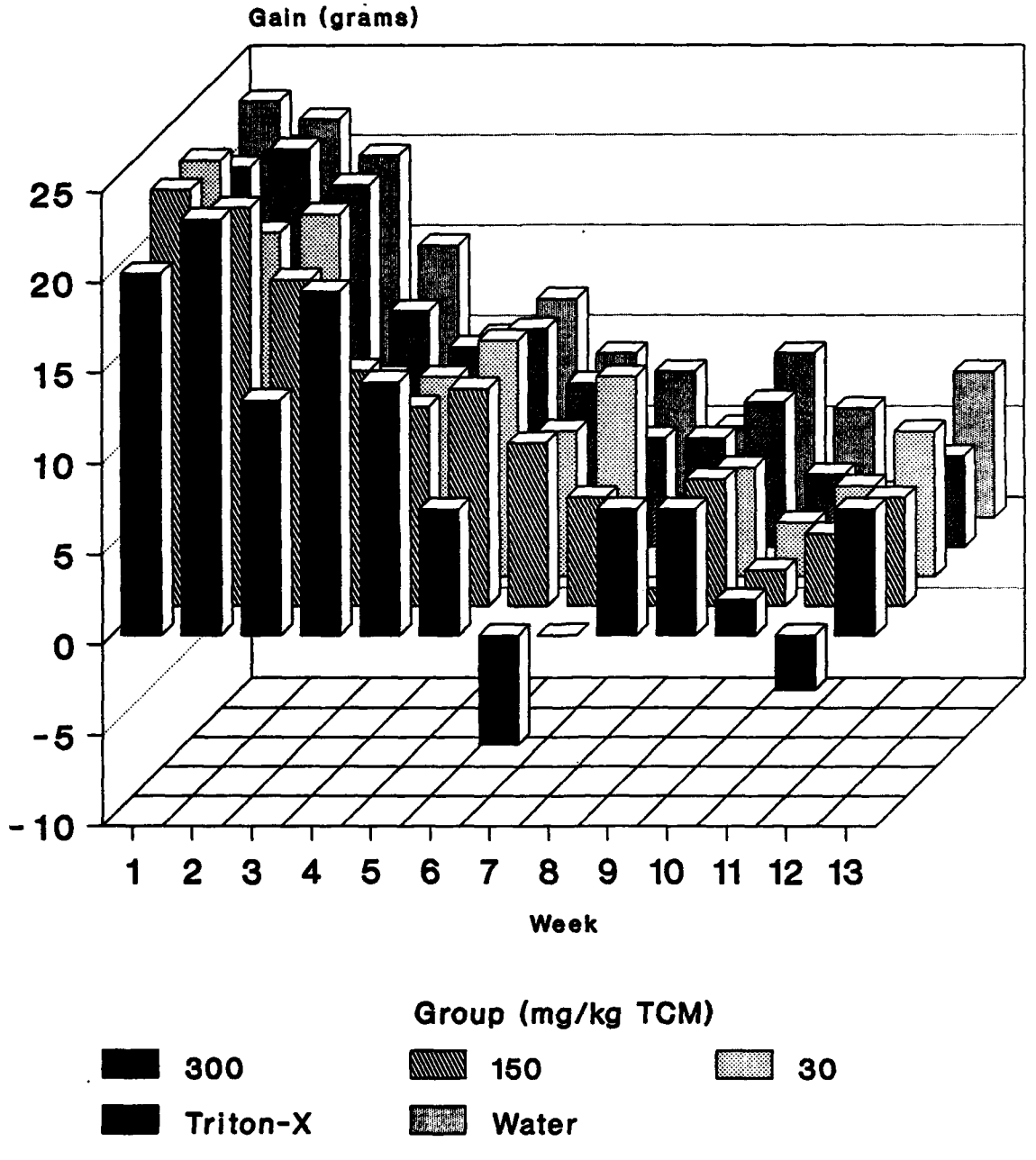
WEEK	GROUP	1 Water	2 Triton-X	3 30mg/kg	4 150mg/kg	5 300mg/kg
1	MEAN	187	184	163	199	183
	S.D.	26.0	12.7	45.7	42.0	13.5
	N	10	10	10	10	10
2	MEAN	206	209	199	202	198
	S.D.	26.5	27.1	16.4	22.8	15.1
	N	10	10	10	10	10
3	MEAN	209	212	203	207	214
	S.D.	25.8	16.7	25.5	32.5	18.9
	N	10	10	10	10	9
4	MEAN	222	226	214	225	224
	S.D.	29.3	20.0	24.3	26.4	29.2
	N	10	10	10	10	9
5	MEAN	222	223	213	226	221
	S.D.	33.7	20.9	26.0	31.7	31.4
	N	10	10	10	10	8
6	MEAN	227	235	222	235	212
	S.D.	36.6	20.2	23.7	42.2	47.3
	N	10	10	10	10	8
7	MEAN	228	237	221	240	214
	S.D.	36.5	21.8	25.6	39.3	45.1
	N	10	10	10	10	7
8	MEAN	236	243	227	241	238
	S.D.	33.4	21.9	27.1	30.0	18.8
	N	10	10	10	10	7
9	MEAN	229	241	191	229	221
	S.D.	36.1	25.2	47.7	29.0	49.1
	N	10	10	10	10	7
10	MEAN	227	216	216	231	230
	S.D.	39.6	31.0	31.0	30.5	38.2
	N	10	10	10	10	6
11	MEAN	229	231	220	231	209
	S.D.	37.5	20.0	31.2	30.5	40.9
	N	10	10	10	10	6
12	MEAN	226	226	213	221	204
	S.D.	40.6	18.1	29.4	36.9	24.7
	N	10	10	10	10	10
13	MEAN	214	220	200	204	201
	S.D.	39.8	21.4	24.9	51.6	19.5
	N	10	10	10	10	6

* Indicates significance at the 0.05 level.

APPENDIX K

90-DAY WEIGHT GAINS/LOSS FOR MALE AND FEMALE RATS

90-DAY TCM STUDY #75-51-0743-88
WEIGHT GAINS - FEMALE RATS

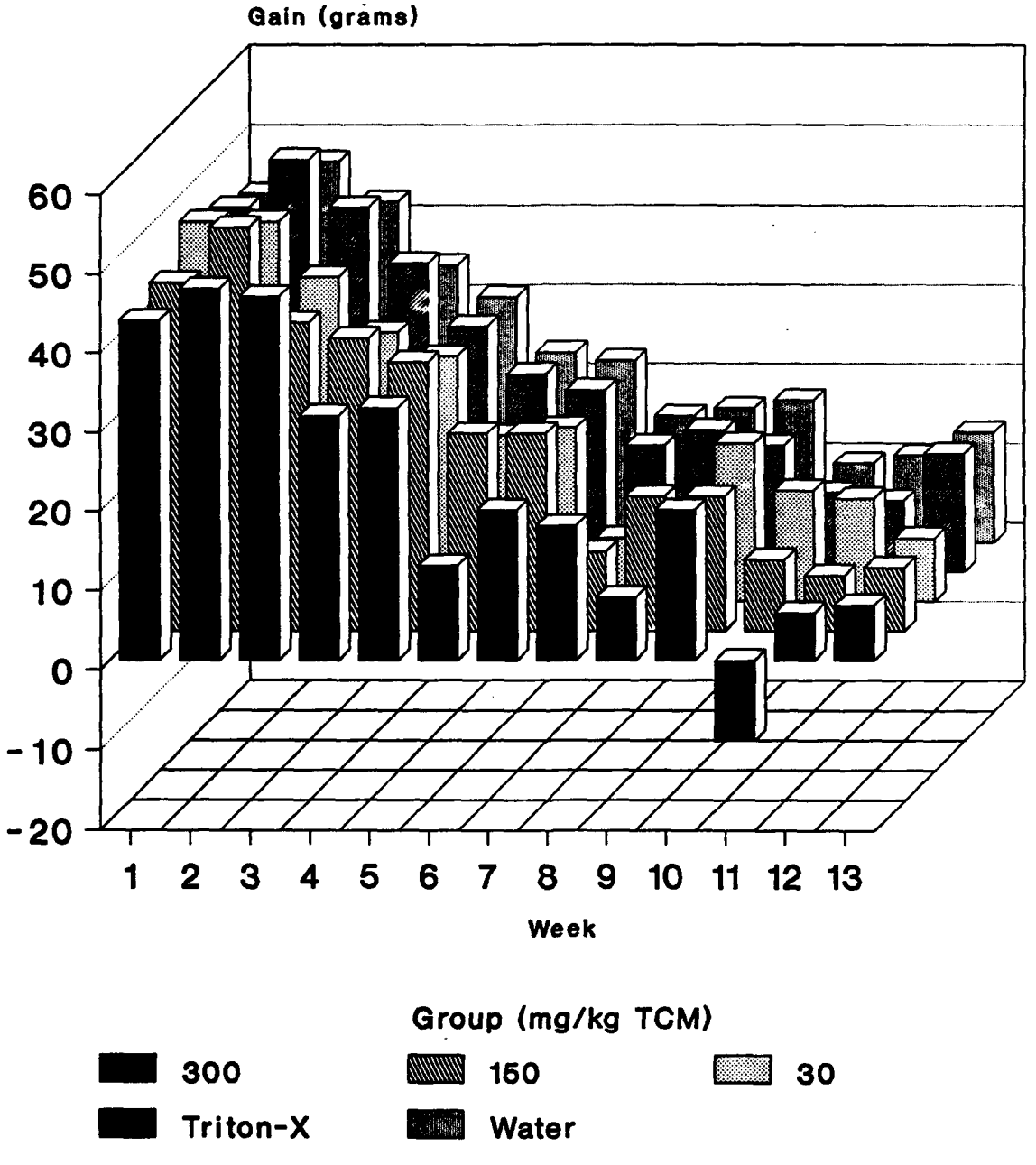


90-DAY TCM STUDY #75-51-0743-88(2)
SUMMARY OF BODY WEIGHT GAINS (GRAMS)
FEMALE RATS

WEEK	GROUP	1 Water	2 Triton-X	3 30mg/kg	4 150mg/kg	5 300mg/kg
1	MEAN	23	21	23	23	20
	S.D.	6.5	5.2	5.0	4.6	8.2
	N	10	10	10	10	9
2	MEAN	22	22	19	22	23
	S.D.	4.6	7.5	5.3	7.0	5.1
	N	10	10	10	10	9
3	MEAN	20	20	20	18	13
	S.D.	5.6	5.0	8.4	5.1	10.8
	N	10	10	10	10	8
4	MEAN	15	13	11	13	19
	S.D.	4.4	4.7	5.7	5.0	7.4
	N	10	10	10	10	7
5	MEAN	10	11	11	11	14
	S.D.	2.9	3.6	4.0	3.7	5.1
	N	10	10	10	10	7
6	MEAN	12	12	13	12	7
	S.D.	6.8	5.8	4.0	6.6	10.1
	N	10	10	10	10	7
7	MEAN	9	9	8	6	-6*
	S.D.	3.1	5.5	7.5	11.9	14.6
	N	10	10	10	10	7
8	MEAN	8	6	11	1	0
	S.D.	6.2	4.0	3.6	16.8	17.8
	N	10	10	10	9	7
9	MEAN	5	6	3	6	7
	S.D.	7.4	5.3	5.6	8.7	9.4
	N	10	10	10	7	10
10	MEAN	9	8	6	7	7
	S.D.	3.8	5.2	5.4	3.2	4.5
	N	10	10	10	7	7
11	MEAN	6	4	3	2	2
	S.D.	2.7	4.9	13.7	6.3	14.5
	N	10	10	10	7	7
12	MEAN	2	3	5	4	-3
	S.D.	3.7	3.4	8.6	7.0	12.2
	N	10	10	10	7	7
13	MEAN	8	5	8	6	7
	S.D.	6.8	3.1	3.5	7.1	5.4
	N	8	10	10	7	6
TOTAL GAIN	MEAN	150	140	141	143	127
	S.D.	18.9	24.2	30.1	29.1	14.5
	N	8	10	10	7	6

* Indicates significance at the 0.05 level.

90-DAY TCM STUDY #75-51-0743-88
WEIGHT GAINS - MALE RATS



90-DAY TCM STUDY #75-51-0743-88(2)
SUMMARY OF BODY WEIGHT GAINS (GRAMS)
MALE RATS

WEEK	GROUP	1 Water	2 Triton-X	3 30mg/kg	4 150mg/kg	5 300mg/kg
1	MEAN	44	46	48	44	43
	S.D.	8.5	8.7	5.6	6.8	9.5
	N	10	10	10	10	9
2	MEAN	48	52	48	51	47
	S.D.	9.5	10.0	10.3	8.5	6.7
	N	10	10	10	10	9
3	MEAN	43	46	41	39	46
	S.D.	9.4	9.0	13.5	15.0	10.6
	N	10	10	10	10	8
4	MEAN	35	39	34	37	31
	S.D.	8.3	8.7	9.2	6.3	14.4
	N	10	10	10	10	7
5	MEAN	31	31	31	34	32
	S.D.	6.3	6.2	5.2	7.4	9.2
	N	10	10	10	10	7
6	MEAN	24	25	21	25	12
	S.D.	7.3	6.5	4.6	12.7	22.1
	N	10	10	10	10	7
7	MEAN	23	23	22	25	19
	S.D.	5.6	5.1	8.7	7.8	28.5
	N	10	10	10	10	7
8	MEAN	16	16	8	10	17
	S.D.	8.0	5.4	11.9	9.8	8.7
	N	10	10	10	9	7
9	MEAN	17	18	7	17	8
	S.D.	5.4	4.3	21.2	11.1	24.4
	N	10	10	10	7	10
10	MEAN	18	16	20	17	19
	S.D.	3.7	4.5	13.3	5.7	7.2
	N	10	10	10	7	7
11	MEAN	10	10	14	9	-10*
	S.D.	5.3	4.3	8.5	10.9	14.5
	N	10	10	10	7	7
12	MEAN	11	9	13	7	6
	S.D.	4.7	4.1	5.8	8.8	10.6
	N	10	10	10	7	7
13	MEAN	14	15	8	8	7
	S.D.	7.6	6.1	10.0	20.4	23.2
	N	8	10	10	7	6
TOTAL GAIN	MEAN	332	346	315	332	284
	S.D.	61.7	54.0	56.6	52.9	47.2
	N	8	10	10	7	6

* Indicates significance at the 0.05 level.

APPENDIX L

90-DAY CLINICAL CHEMISTRY VALUES FOR MALE AND FEMALE RATS

90-DAY TCM STUDY #75-51-0743-88(2)
CLINICAL CHEMISTRY SUMMARY
FEMALE RATS

TEST	GROUP	1 Water	2 Triton-X	3 30mg/kg	4 150mg/kg	5 300mg/kg
ALK. PHOS.	MEAN	196.0	173.9	173.8	277.8	198.6
IU/L	S.D.	56.7	57.2	64.0	115.4	80.8
	N	10	10	10	7	6
SGOT	MEAN	68.1	89.8	90.8	87.8	84.6
IU/L	S.D.	8.9	25.9	24.3	21.5	19.4
	N	10	10	10	7	6
SGPT	MEAN	36.7	50.6	46.0	50.4	41.9
IU/L	S.D.	5.4	22.1	14.1	10.7	14.7
	N	10	10	10	7	6
GLUCOSE	MEAN	146.2	134.4	139.4	127.9	131.0
IU/L	S.D.	32.1	15.9	36.3	13.6	19.4
	N	10	10	10	7	6
TOT. BILI.	MEAN	1.1	1.1	1.0	0.9	0.9
MG/DL	S.D.	0.6	0.4	0.3	0.2	0.4
	N	10	10	10	7	6
BUN	MEAN	21.4	22.3	24.1	21.4	21.2
MG/DL	S.D.	3.5	2.0	5.0	2.4	3.7
	N	10	10	10	7	6
TOT. PROT.	MEAN	8.8	8.8	8.7	8.4	8.2
G/DL	S.D.	0.6	0.6	0.7	0.6	0.7
	N	10	10	10	7	6
CALCIUM	MEAN	12.0	11.5	11.5	10.9*	11.2*
MG/DL	S.D.	0.7	0.4	0.8	0.5	0.5
	N	10	10	10	7	6

* Indicates significance at the 0.05 level.

ALK. PHOS. - Alkaline Phosphatase
SGOT - Serum Glutamic Oxaloacetic Transaminase
SGPT - Serum Glutamic Pyruvic Transaminase
TOT. BILI. - Total Bilirubin
BUN - Blood Urea Nitrogen
TOT. PROT. - Total Protein

90-DAY TCM STUDY #75-51-0743-88 (2)
CLINICAL CHEMISTRY SUMMARY
MALE RATS

TEST	GROUP	1 Water	2 Triton-X	3 30mg/kg	4 150mg/kg	5 300mg/kg
ALK. PHOS.	MEAN	254.8	284.2	258.9	245.9	169.4
IU/L	S.D.	72.4	86.1	107.3	75.4	34.4
	N	10	10	9	10	6
SGOT	MEAN	94.2	86.1	90.7	89.7	77.6
IU/L	S.D.	18.2	19.7	16.9	33.3	13.1
	N	10	10	9	10	6
SGPT	MEAN	42.9	47.9	47.9	48.5	47.5
IU/L	S.D.	7.4	10.2	10.3	6.5	8.8
	N	10	10	9	10	6
GLUCOSE	MEAN	119.1	131.4	130.9	150.3*	117.4
IU/L	S.D.	17.1	16.8	20.8	38.2	5.5
	N	10	10	9	10	6
TOT. BILI.	MEAN	0.8	0.7	0.8	0.6	0.6
MG/DL	S.D.	0.4	0.1	0.2	0.1	0.2
	N	7	6	4	5	4
BUN	MEAN	24.3	25.1	24.0	23.3	23.5
MG/DL	S.D.	5.0	2.9	3.6	2.3	3.4
	N	10	10	9	10	6
TOT. PROT.	MEAN	8.6	8.6	8.5	8.1	7.7*
G/DL	S.D.	0.5	0.5	0.6	0.5	0.7
	N	10	10	9	10	6
CALCIUM	MEAN	10.6	10.8	10.9	10.7	10.3
MG/DL	S.D.	0.6	0.7	0.5	0.8	0.5
	N	10	10	9	10	6

* Indicates significance at the 0.05 level.

ALK. PHOS. - Alkaline Phosphatase
SGOT - Serum Glutamic Oxaloacetic Transaminase
SGPT - Serum Glutamic Pyruvic Transaminase
TOT. BILI. - Total Bilirubin
BUN - Blood Urea Nitrogen
TOT. PROT. - Total Protein

Phase 2, Toxicological Study No. 75-51-0743-88(2), 3 Aug 88 - 17 Jan 89

APPENDIX M

HEMATOLOGY VALUES FOR MALE AND FEMALE RATS

ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - HEMOGLOBIN (g/dL)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 veh cont	3 30mg/kg	4 150mg/kg	5 300mg/kg	6	7	8	9	10	GRAND TOTALS	SUM OF SQUARES
487	474	475	480	478						* 14.9	15.2	14.7	15.7	15.0							1140.63
495	482	476	481	479						* 14.7	15.5	15.2	15.5	15.4							1164.79
503	489	477	483	484						* 15.3	15.3	16.0	14.9	14.0							1142.19
504	492	486	485	490						* 16.2	15.1	15.8	15.3	14.4							1181.54
509	494	491	493	519						* 15.7	14.5	16.3	14.2	15.1							1152.08
510	498	500	499	525						* 14.5	15.4	14.9	16.1	15.9							1181.44
522	501	502	507							* 15.1	15.1	15.3	15.3								924.20
524	511	516								* 15.2	15.2	15.5									702.33
526	512	517								* 15.0	15.7	14.8									690.53
527	513	521								* 15.8	16.0	14.6									718.80
										Totals	152.40	153.00	153.10	107.00	89.80	0.00	0.00	0.00	0.00	0.00	655.30	9998.53
										Observation	10.00	10.00	10.00	7.00	6.00	1.00	1.00	1.00	1.00	1.00	43.00	
										Mean	15.24	15.30	15.31	15.29	14.97	0.00	0.00	0.00	0.00	0.00	15.24	
										Std Dev	0.59	0.32	0.59	0.61	0.62	ERR	ERR	ERR	ERR	ERR		
										# of Group	5											

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	0.55	4	0.14	0.45
Within Groups	11.51	38	0.30	
Totals	12.06	42		

F-table Lookup (num. 4,denom. 38)
F RATIO .05 = 2.62
F RATIO .01 = 3.86

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - HEMOGLOBIN (g/dL)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 veh cont	3 30mg/kg	4 150mg/kg	5 300mg/kg	6	7	8	9	10	GRAND TOTALS	SUM OF SQUARES
379	387	381	382	383						* 14.7	15.4	14.1	14.1	13.5							1033.12
386	389	400	388	385						* 15.9	14.5	15.6	15.4	13.4							1123.14
396	395	404	391	399						* 14.6	15.2	15.5	14.5	14.1							1093.51
402	397	405	392	409						* 15.8	15.3	14.8	15.7	15.5							1189.51
403	401	413	398	414						* 15.2	14.7	14.5	15.6	14.4							1108.10
406	408	425	419	415						* 15.0	15.9	15.6	16.2	15.6							1226.97
407	411	427	421							* 16.0	15.8	15.9	15.7								1004.94
410	416	428	423							* 15.5	15.9	14.8	14.7								928.19
420	418	429	424							* 14.9	14.6	15.5	15.4								912.58
422	426	432	433							* 16.0	15.3	16.0	15.3								980.18
										Totals 153.60	152.60	152.30	152.60	86.50	0.00	0.00	0.00	0.00	0.00	697.60	10600.24
										Observation 10.00	10.00	10.00	10.00	6.00	1.00	1.00	1.00	1.00	1.00	46.00	
										Mean 15.36	15.26	15.23	15.26	14.42	0.00	0.00	0.00	0.00	0.00	15.17	
										Std Dev 0.50	0.46	0.59	0.72	0.87	ERR	ERR	ERR	ERR	ERR		
										# of Group 5											

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	3.96	4	0.99	2.39
Within Groups	17.02	41	0.42	
Totals	20.98	45		

F-table Lookup (num. 4,denom. 41)
F RATIO .05 = 2.60
F RATIO .01 = 3.82

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - HEMATOCRIT (%)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 veh cont	3 30mg/kg	4 150mg/kg	5 300mg/kg	6	7	8	9	10	GRAND TOTALS	SUM OF SQUARES
487	474	475	480	478						* 41.0	42.0	39.0	43.5	41.4							8572.21
495	482	476	481	479						* 42.0	42.6	41.6	43.8	41.4							8941.72
503	489	477	483	484						* 44.3	41.9	43.5	41.3	39.0							8837.04
504	492	486	485	490						* 45.7	43.4	43.6	42.3	40.3							9286.39
509	494	491	493	519						* 45.3	39.4	44.3	38.4	43.2							8907.74
510	498	500	499	525						* 44.2	42.2	42.3	45.1	47.3							9795.07
522	501	502	507							* 45.3	41.7	41.9	44.8								7553.63
524	511	516								* 45.6	43.3	45.3									6006.34
526	512	517								* 45.0	46.8	43.0									6064.24
527	513	521								* 47.1	47.4	43.6									6366.13
										Totals 445.50	430.70	428.10	299.20	252.60	0.00	0.00	0.00	0.00	0.00	1856.10	80330.51
										Observation 10.00	10.00	10.00	7.00	6.00	1.00	1.00	1.00	1.00	1.00	43.00	
										Mean 44.55	43.07	42.81	42.74	42.10	0.00	0.00	0.00	0.00	0.00	43.17	
										Std Dev 1.70	1.23	1.75	2.15	2.65	ERR	ERR	ERR	ERR	ERR		
										# of Group 5											

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	28.59	4	7.15	1.48
Within Groups	183.15	38	4.82	
Totals	211.74	42		

F-table Lookup (num. 4,denom. 38)
F RATIO .05 = 2.62
F RATIO .01 = 3.86

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - HEMATOCRIT (%)

ANIMAL # GROUPS 1	2	3	4	5	6	7	8	9	10	*DATA GROUPS 1 control	2 veh cont	3 30mg/kg	4 150mg/kg	5 300mg/kg	6	7	8	9	10	GRAND TOTALS	SUM OF SQUARES
379	387	381	382	383						43.8	45.4	42.9	42.1	41.7							9331.31
386	389	400	388	385						47.5	43.4	46.8	46.0	40.3							10070.14
396	395	404	391	399						44.2	45.9	46.0	43.6	43.4							9960.97
402	397	405	392	409						49.0	46.7	45.3	48.0	48.1							11251.59
403	401	413	398	414						46.5	45.6	44.1	47.0	44.5							10375.67
406	408	425	419	415						45.6	48.3	47.8	48.2	47.9							11314.74
407	411	427	421							49.2	48.9	47.5	47.3								9305.39
410	416	428	423							47.7	48.8	45.3	44.8								8715.86
420	418	429	424							45.4	44.7	47.2	46.9								8486.70
422	426	432	433							49.0	45.4	47.6	45.9								8834.73
						Totals	467.90	463.10	460.50	459.80	265.90	0.00	0.00	0.00	0.00	0.00	2117.20	97647.10
						Observation	10.00	10.00	10.00	10.00	6.00	1.00	1.00	1.00	1.00	1.00	46.00	
						Mean	46.79	46.31	46.05	45.98	44.32	0.00	0.00	0.00	0.00	0.00	46.03	
						Std Dev	1.81	1.47	1.63	2.26	2.92	ERR	ERR	ERR	ERR	ERR		
						# of Group	5											

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ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	24.20	4	6.05	1.41
Within Groups	176.47	41	4.30	
Totals	200.67	45		

F-table Lookup (num. 4,denom. 41)
F RATIO .05 = 2.60
F RATIO .01 = 3.82

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - RED BLOOD CELLS (10E+6/μL)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 veh cont	3 30mg/kg	4 150mg/kg	5 300mg/kg	6	7	8	9	10	GRAND TOTALS	SUM OF SQUARES
487	474	475	480	478						* 7.5	7.8	7.1	7.6	7.9							287.67
495	482	476	481	479						* 7.7	7.8	7.8	7.9	7.4							298.14
503	489	477	483	484						* 8.0	7.9	7.9	7.7	7.2							299.95
504	492	486	485	490						* 8.5	7.8	7.8	7.5	7.4							304.94
509	494	491	493	519						* 8.1	7.0	8.1	6.9	7.8							288.67
510	498	500	499	525						* 7.7	7.6	7.7	8.4	8.9							326.11
522	501	502	507							* 8.1	7.6	7.7	7.9								245.07
524	511	516								* 8.3	7.8	8.2									196.97
526	512	517								* 8.2	8.7	7.7									202.22
527	513	521								* 8.3	8.6	7.7									202.14
										Totals	80.40	78.60	77.70	53.90	46.60	0.00	0.00	0.00	0.00	0.00	337.20	2651.88
										Observation	10.00	10.00	10.00	7.00	6.00	1.00	1.00	1.00	1.00	1.00	43.00	
										Mean	8.04	7.86	7.77	7.70	7.77	0.00	0.00	0.00	0.00	0.00	7.84	
										Std Dev	0.33	0.30	0.31	0.45	0.56	ERR	ERR	ERR	ERR	ERR		
										# of Group	5											

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	0.62	4	0.16	0.85
Within Groups	6.98	38	0.18	
Totals	7.60	42		

F-table Lookup (num. 4,denom. 38)
F RATIO .05 = 2.62
F RATIO .01 = 3.86

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - RED BLOOD CELLS (10E+6/μL)

ANIMAL # GROUPS 1	2	3	4	5	6	7	8	9	10	*DATA GROUPS 1 control	2 veh cont	3 30mg/kg	4 150mg/kg	5 300mg/kg	6	7	8	9	10	GRAND TOTALS	SUM OF SQUARES
379	387	381	382	383						8.6	8.7	8.7	7.7	7.7							343.92
386	389	400	388	385						9.3	8.3	9.1	8.6	7.4							366.91
396	395	404	391	399						8.2	8.6	9.1	7.9	8.0							350.42
402	397	405	392	409						9.1	9.3	7.9	8.8	8.5							381.40
403	401	413	398	414						8.2	8.2	8.1	9.1	8.5							355.15
406	408	425	419	415						8.5	9.4	9.3	9.5	8.4							407.91
407	411	427	421							9.1	9.2	9.1	8.3								319.15
410	416	428	423							9.3	8.9	9.4	8.5								326.31
420	418	429	424							8.7	8.4	8.7	8.5								294.19
422	426	432	433							9.6	8.8	8.5	8.7								317.54
									Totals	88.60	87.80	87.90	85.60	48.50	0.00	0.00	0.00	0.00	0.00	398.40	3462.90
									Observation	10.00	10.00	10.00	10.00	6.00	1.00	1.00	1.00	1.00	1.00	46.00	
									Mean	8.86	8.78	8.79	8.56	8.08 *	0.00	0.00	0.00	0.00	0.00	8.66	
									Std Dev	0.42	0.46	0.53	0.63	0.42	ERR	ERR	ERR	ERR	ERR		
									# of Group	5											

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ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	2.81	4	0.70	3.00
Within Groups	9.60	41	0.23	
Totals	12.41	45		

F-table Lookup (num. 4,denom. 41)
F RATIO .05 = 2.60
F RATIO .01 = 3.82

CONCLUSIONS: AVERAGES ARE SIGNIFICANTLY DIFFERENT AT .05 LEVEL. *
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - MEAN CELL VOLUME (fL)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 veh cont	3 30mg/kg	4 150mg/kg	5 300mg/kg	6	7	8	9	10	GRAND TOTALS	SUM OF SQUARES
487	474	475	480	478						* 55	54	55	57	52							14919.00
495	482	476	481	479						* 55	55	53	56	56							15131.00
503	489	477	483	484						* 55	53	55	54	54							14691.00
504	492	486	485	490						* 54	56	56	56	54							15240.00
509	494	491	493	519						* 56	56	55	56	55							15458.00
510	498	500	499	525						* 57	56	55	54	53							15135.00
522	501	502	507							* 56	55	54	57								12326.00
524	511	516								* 55	56	55									9186.00
526	512	517								* 55	54	56									9077.00
527	513	521								* 57	55	57									9523.00
										Totals	555.00	550.00	551.00	390.00	324.00	0.00	0.00	0.00	0.00	0.00	2370.00	130686.00
										Observation	10.00	10.00	10.00	7.00	6.00	1.00	1.00	1.00	1.00	1.00	43.00	
										Mean	55.50	55.00	55.10	55.71	54.00	0.00	0.00	0.00	0.00	0.00	55.12	
										Std Dev	0.94	1.15	0.90	1.12	1.29	ERR	ERR	ERR	ERR	ERR		
										# of Group	5											

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	11.59	4	2.90	2.25
Within Groups	48.83	38	1.28	
Totals	60.42	42		

F-table Lookup (num. 4,denom. 38)
F RATIO .05 = 2.62
F RATIO .01 = 3.86

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - MEAN CELL VOLUME (fL)

ANIMAL # GROUPS										*DATA GROUPS										
1	2	3	4	5	6	7	8	9	10	* 1 control	2 veh cont	3 30mg/kg	4 150mg/kg	5 300mg/kg	6	7	8	9	10	GRAND TOTALS	SUM OF SQUARES
379	387	381	382	383						* 51	52	49	55	54							13647.00
386	389	400	388	385						* 51	52	51	54	55							13847.00
396	395	404	391	399						* 54	53	51	55	54							14267.00
402	397	405	392	409						* 54	54	57	55	57							15355.00
403	401	413	398	414						* 57	56	54	52	52							14709.00
406	408	425	419	415						* 54	51	51	51	57							13968.00
407	411	427	421							* 54	53	52	57								11678.00
410	416	428	423							* 51	55	48	53								10739.00
420	418	429	424							* 52	53	54	55								11454.00
422	426	432	433							* 51	52	56	53								11250.00
										Totals 529.00	531.00	523.00	540.00	329.00	0.00	0.00	0.00	0.00	0.00	2452.00	130914.00
										Observation 10.00	10.00	10.00	10.00	6.00	1.00	1.00	1.00	1.00	1.00	46.00	
										Mean 52.90	53.10	52.30	54.00	54.83	0.00	0.00	0.00	0.00	0.00	53.30	
										Std Dev 2.06	1.63	2.61	1.60	1.77	ERR	ERR	ERR	ERR	ERR		
										# of Group 5											

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ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	31.01	4	7.75	1.76
Within Groups	180.73	41	4.41	
Totals	211.74	45		

F-table Lookup (num. 4,denom. 41)
F RATIO .05 = 2.60
F RATIO .01 = 3.82

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - WHITE BLOOD CELLS (10E+3/μL)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 veh cont	3 30mg/kg	4 150mg/kg	5 300mg/kg	6	7	8	9	10	GRAND TOTALS	SUM OF SQUARES
487	474	475	480	478						* 8.9	8.4	6.7	7.3	4.9							271.96
495	482	476	481	479						* 6.3	3.1	7.1	12.5	4.1							272.77
503	489	477	483	484						* 8.0	8.6	6.5	8.9	6.0							295.42
504	492	486	485	490						* 10.3	3.9	10.6	9.7	12.5							484.00
509	494	491	493	519						* 10.8	10.7	10.1	8.2	7.5							456.63
510	498	500	499	525						* 10.3	9.5	7.5	8.4	18.5							665.40
522	501	502	507							* 8.1	8.8	7.8	5.9								238.70
524	511	516								* 17.6	6.3	10.9									468.26
526	512	517								* 6.2	8.6	8.0									176.40
527	513	521								* 11.4	12.1	8.2									343.61
										Totals	97.90	80.00	83.40	60.90	53.50	0.00	0.00	0.00	0.00	0.00	375.70	3673.15
										Observation	10.00	10.00	10.00	7.00	6.00	1.00	1.00	1.00	1.00	1.00	43.00	
										Mean	9.79	8.00	8.34	8.70	8.92	0.00	0.00	0.00	0.00	0.00	8.74	
										Std Dev	1.57	2.84	1.64	1.66	5.07	ERR	ERR	ERR	ERR	ERR		
										# of Group	5											

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	18.30	4	4.57	0.47
Within Groups	372.28	38	9.80	
Totals	390.58	42		

F-table Lookup (num. 4,denom. 38)
F RATIO .05 = 2.62
F RATIO .01 = 3.86

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - WHITE BLOOD CELLS (10E+3/μL)

ANIMAL # GROUPS										*DATA GROUPS											
1	2	3	4	5	6	7	8	9	10	* 1 control	2 veh cont	3 30mg/kg	4 150mg/kg	5 300mg/kg	6	7	8	9	10	GRAND TOTALS	SUM OF SQUARES
379	387	381	382	383						* 10.4	19.8	10.9	11.3	7.0							795.70
386	389	400	388	385						* 10.9	14.4	13.5	18.5	9.0							931.67
396	395	404	391	399						* 16.5	12.3	11.3	17.3	9.7							944.61
402	397	405	392	409						* 10.1	23.1	12.9	14.8	19.0							1382.07
403	401	413	398	414						* 12.3	18.9	7.5	12.8	14.5							938.84
406	408	425	419	415						* 10.7	10.0	9.2	19.1	16.2							926.38
407	411	427	421							* 20.0	13.9	18.5	22.6								1446.22
410	416	428	423							* 13.8	14.2	8.0	11.5								588.33
420	418	429	424							* 13.3	12.3	14.3	11.0								653.67
422	426	432	433							* 12.7	10.8	17.1	9.2								654.98
										Totals	130.70	149.70	123.20	148.10	75.40	0.00	0.00	0.00	0.00	0.00	627.10	9262.47
										Observation	10.00	10.00	10.00	10.00	6.00	1.00	1.00	1.00	1.00	1.00	46.00	
										Mean	13.07	14.97	12.32	14.81	12.57	0.00	0.00	0.00	0.00	0.00	13.63	
										Std Dev	2.21	4.55	2.06	2.90	4.29	ERR	ERR	ERR	ERR	ERR		
										# of Group	5											

ANALYSIS OF VARIANCE TABLE

Source	Sum of Squares	Deg. of Freedom	Mean Square	F Ratio
Between Groups	58.96	4	14.74	0.92
Within Groups	654.50	41	15.96	
Totals	713.46	45		

F-table Lookup (num. 4,denom. 41)
F RATIO .05 = 2.60
F RATIO .01 = 3.82

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

Phase 2, Toxicological Study No. 75-51-0743-88(2), 3 Aug 88 - 17 Jan 89

APPENDIX N

90-DAY SUMMARY OF ORGAN WEIGHTS FOR MALE AND FEMALE RATS

90-DAY TCM STUDY #75-51-0743-88(2)
SUMMARY OF ORGAN WEIGHTS (GRAMS)
FEMALE RATS

ORGAN	GROUP	1 Water	2 Triton-X	3 30mg/kg	4 150mg/kg	5 300mg/kg
Body Weight	MEAN	311	301	300	303	286
	S.D.	26.1	25.7	35.0	28.0	21.5
	N	10	10	10	7	5
Brain	MEAN	1.91	1.88	1.81	1.96	1.90
	S.D.	0.087	0.070	0.354	0.055	0.043
	% BODY WT	0.62	0.63	0.60	0.65	0.67
	S.D.	0.044	0.060	0.115	0.078	0.054
	N	10	10	10	7	5
Adrenals	MEAN	0.080	0.078	0.079	0.084	0.085
	S.D.	0.015	0.018	0.018	0.009	0.027
	% BODY WT	0.026	0.026	0.026	0.028	0.029
	S.D.	0.005	0.006	0.005	0.002	0.008
	% BRAIN WT	4.208	4.145	4.696	4.266	4.479
	S.D.	0.845	0.877	2.167	0.539	1.545
	N	10	10	10	7	5
Kidneys	MEAN	2.15	2.22	2.23	2.26	2.19
	S.D.	0.183	0.274	0.388	0.120	0.212
	% BODY WT	0.69	0.74	0.74	0.75	0.77
	S.D.	0.055	0.099	0.079	0.052	0.085
	% BRAIN WT	112.08	117.83	130.08	115.07	115.24
	S.D.	7.543	11.965	45.717	8.095	9.237
	N	10	10	10	7	5
Ovaries	MEAN	0.14	0.14	0.12	0.15	0.28
	S.D.	0.019	0.038	0.027	0.014	0.339
	% BODY WT	0.04	0.05	0.04	0.05	0.10
	S.D.	0.009	0.010	0.009	0.006	0.129
	% BRAIN WT	7.08	7.28	7.46	7.43	14.87
	S.D.	1.138	1.911	4.200	0.738	17.623
	N	10	10	10	7	5
Liver	MEAN	10.45	10.60	10.87	11.20	11.18
	S.D.	1.452	1.131	1.925	1.437	0.612
	% BODY WT	3.35	3.53	3.61	3.69	3.92 *
	S.D.	0.301	0.295	0.376	0.245	0.300
	% BRAIN WT	546.57	565.14	629.45	571.89	589.24
	S.D.	73.138	61.919	198.179	82.977	46.163
	N	10	10	10	7	5
Spleen	MEAN	0.55	0.53	0.54	0.60	0.53
	S.D.	0.093	0.078	0.066	0.068	0.051
	% BODY WT	0.18	0.18	0.18	0.20	0.19
	S.D.	0.031	0.035	0.019	0.020	0.029
	% BRAIN WT	28.84	28.03	31.36	30.47	28.09
	S.D.	4.662	4.146	9.473	3.875	2.452
	N	10	10	10	7	5

* Indicates significance at the 0.05 level.

90-DAY TCM STUDY #75-51-0743-88(2)
SUMMARY OF ORGAN WEIGHTS (GRAMS)
MALE RATS

ORGAN	GROUP	1 Water	2 Triton-X	3 30mg/kg	4 150mg/kg	5 300mg/kg
Body Weight	MEAN	529	534	507	514	477
	S.D.	69.4	65.8	62.9	53.7	46.6
	N	10	10	10	10	10
Brain	MEAN	2.00	1.97	1.96	1.97	2.00
	S.D.	0.061	0.078	0.055	0.065	0.074
	% BODY WT	0.38	0.37	0.39	0.39	0.42
	S.D.	0.055	0.037	0.044	0.034	0.044
	N	10	9	10	10	6
Adrenals	MEAN	0.065	0.061	0.062	0.069	0.069
	S.D.	0.011	0.021	0.009	0.010	0.022
	% BODY WT	0.01	0.01	0.01	0.01	0.01
	S.D.	0.002	0.003	0.003	0.003	0.004
	% BRAIN WT	3.25	3.07	3.15	3.52	3.44
	S.D.	0.610	0.979	0.447	0.494	1.115
	N	10	9	10	10	6
Kidneys	MEAN	3.49	3.65	3.46	3.55	3.34
	S.D.	0.406	0.563	0.368	0.274	0.432
	% BODY WT	0.67	0.68	0.69	0.70	0.70
	S.D.	0.081	0.064	0.070	0.079	0.29
	% BRAIN WT	175.09	184.77	176.56	180.39	166.77
	S.D.	21.789	25.208	18.506	12.106	21.848
	N	10	9	10	10	6
Testes	MEAN	3.53	3.40	3.46	3.45	3.33
	S.D.	0.30	0.139	0.305	0.237	0.180
	% BODY WT	0.67	0.64	0.69	0.68	.70
	S.D.	0.069	0.066	0.102	0.073	0.088
	% BRAIN WT	176.86	172.54	176.31	175.46	166.11
	S.D.	15.831	3.811	15.000	11.827	9.212
	N	10	9	10	10	6
Liver	MEAN	20.42	21.09	18.09	20.24	17.81
	S.D.	4.410	5.438	3.241	3.592	2.849
	% BODY WT	3.83	3.90	3.55	3.92	3.72
	S.D.	0.386	0.620	0.256	0.500	0.395
	% BRAIN WT	1027.49	1063.92	923.26	1027.42	888.80
	S.D.	251.134	244.672	165.451	186.092	145.690
	N	10	9	10	10	6
Spleen	MEAN	0.79	0.86	0.86	0.81	0.70
	S.D.	0.168	0.190	0.109	0.129	0.142
	% BODY WT	0.15	0.16	0.17	0.16	0.15
	S.D.	0.028	0.019	0.019	0.030	0.029
	% BRAIN WT	39.47	43.17	43.68	41.51	34.92
	S.D.	8.702	8.194	5.086	7.175	6.958
	N	10	9	10	10	6

* Indicates significance at the 0.05 level.